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09-10-02

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=> b medline caplus lifesci embase uspatfull biosis

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=> s ssre or (shear stress response element)

L1          106 SSRE OR (SHEAR STRESS RESPONSE ELEMENT)

=> dup rem l1

PROCESSING COMPLETED FOR L1
L2           50 DUP REM L1 (56 DUPLICATES REMOVED)

=>

=> s l2 and decoy

L3            2 L2 AND DECOY

=> d l3 ibib abs tot


L3   ANSWER 1 OF 2     MEDLINE
ACCESSION NUMBER:    1999162459     MEDLINE
DOCUMENT NUMBER:     99162459   PubMed ID: 10051691
TITLE:               Select de novo gene and protein expression during renal
                     epithelial cell culture in rotating wall vessels is shear
                     stress dependent.
AUTHOR:              Kaysen J H; Campbell W C; Majewski R R; Goda F O; Navar G
                     L; Lewis F C; Goodwin T J; Hammond T G
CORPORATE SOURCE:    Nephrology Section, Department of Medicine and Tulane
                     Environmental Astrobiology Center, Tulane/Xavier Center
for
                     Bioenvironmental Research, 1430 Tulane Avenue, New
Orleans,
                     LA 70112, USA.
CONTRACT NUMBER:     DK46117 (NIDDK)
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R21 RR12645 (NCRR)

SOURCE: JOURNAL OF MEMBRANE BIOLOGY, (1999 Mar 1) 168 (1) 77-89.
Journal code: 0211301. ISSN: 0022-2631.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990504
Last Updated on STN: 19990504
Entered Medline: 19990422

AB The rotating wall vessel has gained popularity as a clinical cell culture tool to produce hormonal implants. It is desirable to understand the mechanisms by which the rotating wall vessel induces genetic changes, if we are to prolong the useful life of implants. During rotating wall vessel culture gravity is balanced by equal and opposite hydrodynamic forces including shear stress. The current study provides the first evidence that shear stress response elements, which modulate gene expression in endothelial cells, are also active in epithelial cells. Rotating wall culture of renal cells changes expression of select gene products including the giant glycoprotein scavenger receptors cubulin and megalin, the structural microvillar protein villin, and classic shear stress response genes ICAM, VCAM and MnSOD. Using a putative endothelial cell **shear stress response element** binding site as a **decoy**, we demonstrate the role of this sequence in the regulation of selected genes in epithelial cells. However, many of the changes observed in the rotating wall vessel are independent of this response element. It remains to define other genetic response elements modulated during rotating wall vessel culture, including the role of hemodynamics characterized by 3-dimensionality, low shear and turbulence, and cospatial relation of dissimilar cell types.

L3 ANSWER 2 OF 2 USPATFULL
ACCESSION NUMBER: 2002:99432 USPATFULL
TITLE: Therapeutic use of cis-element decoys in vivo
INVENTOR(S): Dzau, Victor J., Los Altos Hills, CA, UNITED STATES
Gibbons, Gary H., Palo Alto, CA, UNITED STATES
Morishita, Ryuichi, Palo Alto, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002052333	A1	20020502
APPLICATION INFO.:	US 2001-839752	A1	20010419 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-524206, filed on 8 Sep 1995, PENDING Continuation of Ser. No. US 1993-144717, filed on 29 Oct 1993, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 176 FEDERAL STREET, BOSTON, MA, 02110-2214
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 689
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides for the use of oligodeoxynucleotide decoys for the prophylactic or therapeutic treatment of diseases associated with the binding of endogenous transcription factors to genes involved in cell growth, differentiation and signalling or to viral genes. By inhibiting endogenous trans-activating factors from binding transcription regulatory regions, the decoys modulate gene expression

and thereby regulating pathological processes including inflammation, intimal hyperplasia, angiogenesis, neoplasia, immune responses and viral infection. The decoys are administered in amounts and under conditions whereby binding of the endogenous transcription factor to the endogenous gene is effectively competitively inhibited without significant host toxicity. The subject compositions comprise the **decoy** molecules in a context which provides for pharmacokinetics sufficient for effective therapeutic use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d history

(FILE 'HOME' ENTERED AT 11:21:42 ON 10 SEP 2002)

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL, BIOSIS' ENTERED AT 11:21:59 ON 10 SEP 2002

L1 106 S SSRE OR (SHEAR STRESS RESPONSE ELEMENT)
L2 50 DUP REM L1 (56 DUPLICATES REMOVED)
L3 2 S L2 AND DECOY

=> s l2 not l3

L4 48 L2 NOT L3

=> d l4 ibib abs tot

L4 ANSWER 1 OF 48 MEDLINE
ACCESSION NUMBER: 2001559794 IN-PROCESS
DOCUMENT NUMBER: 21518042 PubMed ID: 11605517
TITLE: The study on the shear stress responsive element in endothelial cells.
AUTHOR: Zhang W; Chen H
CORPORATE SOURCE: Institute of Biomedical Engineering, West China University of Medical Sciences, Chengdu 610041.
SOURCE: SHENG WU I HSUEH KUNG CHENG HSUEH TSA CHIH [JOURNAL OF BIOMEDICAL ENGINEERING], (2001 Sep) 18 (3) 461-5. Journal code: 9426398. ISSN: 1001-5515.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20011022
Last Updated on STN: 20020122

AB Vascular endothelial cells, by virtue of their unique anatomical position, are constantly exposed to the fluid mechanical forces generated by flowing blood. The fluid forces could influence endothelial cell's gene expression. At a molecular level, fluid shear stress is known to increase or decrease the expression of a wide variety of genes. The shear stress responsive element (**SSRE**) was proposed after the identification of the first **SSRE**, the GAGACC sequence identified in the platelet-derived growth factor (PDGF) B chain promoter and subsequently identified in other genes whose promoters respond to shear stress. In addition, there are the existence of other positive shear responsive regulatory elements. There is a report on the activation of these promoters in vitro and in vivo and propose an application of these mechanically inducible promoters in the treatment of vascular diseases.

L4 ANSWER 2 OF 48 MEDLINE

ACCESSION NUMBER: 2000467359 MEDLINE
DOCUMENT NUMBER: 20473754 PubMed ID: 11015612
TITLE: Mechanical culture conditions effect gene expression: gravity-induced changes on the space shuttle.
AUTHOR: Hammond T G; Benes E; O'Reilly K C; Wolf D A; Linnehan R M;
Taher A; Kaysen J H; Allen P L; Goodwin T J
CORPORATE SOURCE: Nephrology Section, Department of Medicine, Tulane/Veterans
Affairs Environmental Astrobiology Center, New Orleans, Louisiana 70112, USA.. thammond@mailhost.tcs.tulane.edu
CONTRACT NUMBER: R21-RR-12645 (NCRR)
SOURCE: PHYSIOLOGICAL GENOMICS, (2000 Sep 8) 3 (3) 163-73.
Journal code: 100894125. ISSN: 1094-8341.
Flight Experiment; STS-90 Shuttle Project.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20011024
Entered Medline: 20010308

AB Three-dimensional suspension culture is a gravity-limited phenomenon. The balancing forces necessary to keep the aggregates in suspension increase directly with aggregate size. This leads to a self-propagating cycle of cell damage by balancing forces. Cell culture in microgravity avoids this trade-off. We determined which genes mediate three-dimensional culture of cell and tissue aggregates in the low-shear stress, low-turbulent environment of actual microgravity. Primary cultures of human renal cortical cells were flown on the space shuttle. Cells grown in microgravity and ground-based controls were grown for 6 days and fixed. RNA was extracted, and automated gene array analysis of the expression of 10, 000 genes was performed. A select group of genes were regulated in microgravity. These 1,632 genes were independent of known **shear stress response element**-dependent genes and heat shock proteins. Specific transcription factors underwent large changes in microgravity including the Wilms' tumor zinc finger protein, and the vitamin D receptor. A specific group of genes, under the control of defined transcription factors, mediate three-dimensional suspension culture under microgravity conditions.

L4 ANSWER 3 OF 48 MEDLINE
ACCESSION NUMBER: 2000455429 MEDLINE
DOCUMENT NUMBER: 20303090 PubMed ID: 10842092
TITLE: Molecular events caused by mechanical stress in bone.
AUTHOR: Nomura S; Takano-Yamamoto T
CORPORATE SOURCE: Department of Pathology, Osaka University Medical School 2-2 Yamada-oka, Suita, Osaka, Japan.
SOURCE: MATRIX BIOLOGY, (2000 May) 19 (2) 91-6. Ref: 48
Journal code: 9432592. ISSN: 0945-053X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000926

AB The shape of bone changes as a result of bone remodeling corresponding to physical circumstances such as mechanical stress. The tissue which receives the loaded mechanical stress most efficiently is bone matrix. Recent studies revealed the function of osteocytes as mechanosensors in the early stage of bone remodeling. Loaded mechanical stress is converted

to a series of biochemical reactions, and finally activates osteoclasts and osteoblasts to cause bone resorption and formation. Biochemical and molecular biological studies have recently resulted in the identification of the gene of which expression level is changed by mechanical stress. Nitric oxide (NO) and cAMP is secreted in response to mechanical stress in the immediate early stage. Genes encoding enzymes such as glutamate/aspartate transporter (GLAST), nitric oxide synthetase (NOS) and prostaglandin G/H synthetase (PGHS-2) are identified as mechanical stress-responsive. The expression level of IGF-I is enhanced under the control of PTH/PTHrP. The expression of c-fos is increased by loading of mechanical stress. AP1, a heterodimer of c-FOS/c-JUN, functions as a transcription factor of downstream gene(s). Elements including AP1 sites, cyclic AMP response elements (CRE) and shear stress response elements (**SSRE**) are found in the promoter region of mechanical stress-response genes. The enhanced expression of osteopontin (OPN) in the osteocytes of bone resorption sites was demonstrated by in situ hybridization and immunohistochemistry and transdifferentiation of chondrocytes with the abundant expression of BMP-2 and -4 in the process of distraction osteogenesis was observed.

L4 ANSWER 4 OF 48 MEDLINE
ACCESSION NUMBER: 2000183263 MEDLINE
DOCUMENT NUMBER: 20183263 PubMed ID: 10720423
TITLE: Arterial shear stress stimulates surface expression of the endothelial glycoprotein Ib complex.
AUTHOR: Beacham D A; Lian J; Wu G; Konkle B A; Ludlow L B; Shapiro S S
CORPORATE SOURCE: Cardeza Foundation for Hematologic Research, Department of Medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania 19107-5099, USA.. Dorothy.Beacham@mail.tju.edu
CONTRACT NUMBER: HL09163 (NHLBI)
HL51415 (NHLBI)
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (1999 Jun 15) 73 (4) 508-21.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000317

AB Exposure to shear stress has been shown to alter the expression of a number of surface components of cultured endothelial cells (EC). However, relatively few studies have examined the status of human EC surface proteins after prolonged flow, more closely corresponding to the steady state in vivo. Since the promoter region of glycoprotein (Gp) Ib alpha contains several copies of a putative **shear stress response element**, 5'-GAGACC-3', we investigated the response of cultured human umbilical vein EC (HUVEC) GpIb alpha to shear stress over a 72 h time period. In response to 30 dynes/cm2 of shear stress, total cell content of GpIb alpha protein was markedly increased above static levels at 7 and 24 h, as determined immunohistochemically. Western blot analysis of whole cell lysates after 24, 48, and 72 h of shear treatment demonstrated a 2.4-, 4.1-, and 3.2-fold increase in total GpIb alpha protein, respectively. Cell surface protein expression of GpIb alpha increased 2.5-fold at 7 h, as measured by quantitative immunofluorescence, and remained at that level at 24 h. After 48 h of shear stress, cell surface GpIb alpha, GpIX, and GpV, analyzed by flow cytometric analysis, were further increased over the levels observed at 24

h. The increase in cell surface membrane expression of GPIb alpha at 24, 48, and 72 h was confir[redacted] by immunoprecipitation of bio[redacted]ylated surface proteins. No upregulation of GpIb alpha was noted after exposure to shear stress of 1-3 dynes/cm2. These observations imply that under steady-state arterial shear conditions endothelial expression of the GpIb complex is significantly greater than observed in static EC cultures, and raise the possibility of a more important role for this complex under flow, rather than static conditions.

L4 ANSWER 5 OF 48 MEDLINE
ACCESSION NUMBER: 2000108923 MEDLINE
DOCUMENT NUMBER: 20108923 PubMed ID: 10642296
TITLE: Endothelin-dependent and -independent components of strain-activated brain natriuretic peptide gene transcription require extracellular signal regulated kinase and p38 mitogen-activated protein kinase.
AUTHOR: Liang F; Lu S; Gardner D G
CORPORATE SOURCE: Metabolic Research Unit and Department of Medicine, University of California at San Francisco, 94146-0540, USA.
CONTRACT NUMBER: HL-35753 (NHLBI)
SOURCE: HYPERTENSION, (2000 Jan) 35 (1 Pt 2) 188-92. Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000218
Last Updated on STN: 20000218
Entered Medline: 20000207

AB The application of mechanical strain to cultured cardiac myocytes in vitro leads to activation of the brain natriuretic peptide (BNP) gene promoter, a marker of cardiac hypertrophy. We have previously shown that this activation results from both a direct mechanostimulatory event and an indirect autocrine/paracrine stimulation involving the sequential production of angiotensin II and endothelin (ET). In the present study, we examined the role of p38 mitogen-activated protein kinase (MAPK) and extracellular signal regulated kinase (ERK) in signaling the increase in promoter activity trafficking through each of these pathways. ET was shown to stimulate both p38 MAPK and ERK activity in these cultures and to activate human BNP (hBNP) promoter activity. Activation of the promoter was inhibited approximately 45% by SB-203580, a p38 MAPK inhibitor, and approximately 70% by PD98059, an inhibitor of the ERK-activating kinase MAPK kinase. The ET-independent (ie, direct) stimulation of the hBNP promoter by mechanical strain was inhibited approximately 70% by SB-203580 and approximately 60% by PD98059, implying that similar signaling circuitry is used, albeit to different degrees, by the direct and indirect pathways. The p38 MAPK component of both the ET-dependent and the ET-independent responses to strain appears to operate through a series of nuclear factor-kappaB binding, **shear stress response element**-like structures in the hBNP gene promoter. Collectively, these data suggest that activation of the BNP promoter by hypertrophic stimuli involves the participation of several independent signaling pathways. Such redundancy would help to guarantee generation of the full hypertrophic phenotype independently of the nature of the hypertrophic stimulus.

L4 ANSWER 6 OF 48 MEDLINE
ACCESSION NUMBER: 2000075753 MEDLINE

DOCUMENT NUMBER: 20075753 PubMed ID: 10609662
TITLE: Delivery and expression of fluid shear stress-inducible promoters to the vessel wall: applications for cardiovascular gene therapy.
AUTHOR: Houston P; White B P; Campbell C J; Braddock M
CORPORATE SOURCE: Endothelial Cell Gene Expression Group, Vascular Diseases Unit, Glaxo Wellcome Medicines Research Centre, Stevenage, Herts, England.
SOURCE: HUMAN GENE THERAPY, (1999 Dec 10) 10 (18) 3031-44.
Journal code: 9008950. ISSN: 1043-0342.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000106

AB In atherosclerosis, endothelial cells at sites of stenosis experience elevated levels of shear stress. We have constructed a series of shear stress-inducible transcription units (SITUs) expressing the luciferase reporter gene and determined their activation by fluid shear stress in transfected endothelial cells. Chimeric promoters were constructed that comprised basal transcription factor-binding sites coupled to a **shear stress response element** (**SSRE**). We have used consensus binding sites for transcription factors NF-kappaB, Ap1, Sp1, Oct1, and Egr-1/Sp1 in either the presence or absence of the previously defined "GAGACC" **SSRE**. The response of the promoters to shear stress was determined after transfection into human umbilical vein endothelial cells (HUVECs). After transient transfection into HUVECs, fluid shear stress activated the promoters by between two- and eightfold. The most responsive SITUs comprised an overlapping Sp1/Egr-1-binding site linked to a TATA box with (SP5) or without (SP7) the GAGACC **SSRE**. Instillation of SP5 DNA in vivo into the left carotid artery of rabbit and subsequent generation of a stenosis using a mechanical wire occluder caused a 10-fold upregulation of luciferase reporter gene expression at the site of vessel occlusion. These vectors show promise for therapeutic gene expression at sites of occlusive vascular disease.

L4 ANSWER 7 OF 48 MEDLINE
ACCESSION NUMBER: 1999057940 MEDLINE
DOCUMENT NUMBER: 99057940 PubMed ID: 9837956
TITLE: Genomic organization and regulation of expression of the lectin-like oxidized low-density lipoprotein receptor (LOX-1) gene.
AUTHOR: Nagase M; Abe J; Takahashi K; Ando J; Hirose S; Fujita T
CORPORATE SOURCE: Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Bunkyo-ku, Tokyo 112-0015, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Dec 11) 273 (50) 33702-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
OTHER SOURCE: GENBANK-AB018097; GENBANK-AB018098; GENBANK-AB018099; GENBANK-AB018100; GENBANK-AB018101; GENBANK-AB018102; GENBANK-AB018103; GENBANK-AB018104
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990114

AB Lectin-like oxidized low-density lipoprotein receptor (LOX-1) is a recently identified receptor for oxidized low-density lipoprotein, one of the major atherogenic substances. Although LOX-1 was reported to be expressed abundantly in endothelial cells, including atheromatous lesions, the regulation of LOX-1 gene has not yet been clarified. In the present study, we isolated the rat LOX-1 gene and investigated the regulation of gene expression. The rat LOX-1 gene was encoded by a single copy gene spanning over 19 kilobases and consisted of eight exons. Exon boundaries correlated well with the functional domain boundaries of the receptor protein. The promoter region contained putative TATA and CAAT boxes and multiple cis-elements such as NF-kappaB, AP-1 and AP-2 sites, and a **shear stress response element.** Northern blot analysis revealed that LOX-1 gene expression was up-regulated 9-fold by shear stress, 21-fold by lipopolysaccharide, and 4-fold by tumor necrosis factor-alpha, in cultured vascular endothelial cells. LOX-1 was also expressed in macrophages but not in vascular smooth muscle cells. These data provide important information for elucidating the molecular mechanisms of LOX-1 gene regulation and suggest a role for LOX-1 in the pathophysiology of atherosclerotic cardiovascular disease.

L4 ANSWER 8 OF 48 MEDLINE
ACCESSION NUMBER: 1998405866 MEDLINE
DOCUMENT NUMBER: 98405866 PubMed ID: 9736459
TITLE: Shear stress down-regulates gene transcription and production of adrenomedullin in human aortic endothelial cells.
AUTHOR: Shinoki N; Kawasaki T; Minamino N; Okahara K; Ogawa A; Ariyoshi H; Sakon M; Kambayashi J; Kangawa K; Monden M
CORPORATE SOURCE: Department of Surgery II, Osaka University Medical School, Suita, Japan.
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (1998 Oct 1) 71 (1) 109-15.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981117

AB Vascular endothelial cells are potent modulators of vascular tone in response to shear stress. Levels of vasoactive peptides such as adrenomedullin (AM), endothelin-1 (ET-1), C-type natriuretic peptide (CNP), and nitric oxide (NO) are affected by fluid shear stress. AM, a potent vasodilator and suppressor of smooth muscle cell proliferation, contains the shear stress responsive element (**SSRE**) "GAGACC" in its promoter region. To examine the role of AM in the shear stress response, cultured human aortic endothelial cells (HAoECs) were exposed to fluid shear stresses of 12 and 24 dynes/cm2 in a cone-plate shear stress loading apparatus for various time periods, and the levels of AM gene expression and peptide secretion from HAoECs were measured by Northern blotting analysis and radioimmunoassay (RIA), respectively. Both AM gene transcription and AM peptide levels were down-regulated by fluid shear stress in a time- and magnitude-dependent manner. Our results demonstrate that the normal level of arterial shear stress down-regulates AM expression in HAoECs, suggesting that AM participates in the modulation of vascular tone by fluid shear stress.

L4 ANSWER 9 OF 48 MEDLINE
ACCESSION NUMBER: 1998173337 MEDLINE

DOCUMENT NUMBER: 98173337 PubMed ID: 9514402
TITLE: Regulation of PDGF-B in endothelial cells exposed to cyclic strain.
AUTHOR: Sumpio B E; Du W; Galagher G; Wang X; Khachigian L M; Collins T; Gimbrone M A Jr; Resnick N
CORPORATE SOURCE: Department of Surgery (Vascular), Yale University School of Medicine, New Haven, Conn 06510, USA.. bauer.sumpio@yale.edu
CONTRACT NUMBER: R01HL47345 (NHLBI)
SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (1998 Mar) 18 (3) 349-55.
Journal code: 9505803. ISSN: 1079-5642.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980410
Last Updated on STN: 20000303
Entered Medline: 19980402

AB The present study was designed to examine the regulation by cyclic strain of endothelial cell (EC) platelet-derived growth factor-B chain (PDGF-B) expression. We demonstrate in this study that bovine aortic ECs subjected to 10% (but not 6%) average strain resulted in a 2.6-fold increase in PDGF-B steady state mRNA and immunoreactive protein. Nuclear runoff transcription assays confirmed the induction of PDGF-B transcripts. To address the regulation of PDGF-B gene expression by cyclic strain, we transfected bovine aortic ECs with a construct containing 450 bp of human PDGF-B promoter sequence coupled to chloramphenicol acetyltransferase (CAT), and found that subjecting these cells to 10% average strain resulted in a twofold increase in CAT activity by 4 hours. Analysis of nested 5' deletions of the promoter transfected into ECs demonstrated a 55% drop-off in activity between position -313 and -153, with no induction of activity with the - 101-bp minimal promoter. Since a **shear stress response element** (**SSRE**) is located at position -125, we tested the hypothesis that the **SSRE** site was necessary and/or sufficient for induction of PDGF-B activity with strain. Electromobility shift assays revealed that nuclear proteins from ECs exposed to strain for short intervals (30 minutes) bound to the PDGF-B **SSRE**. However, transfection of ECs with hybrid promoter constructs containing the SV40 sequence promoter downstream of the **SSRE** or the -153 PDGF-B promoter sequence bearing a mutation in the **SSRE** demonstrated that the **SSRE** was not necessary for inducible reporter gene expression in ECs exposed to cyclic strain.

L4 ANSWER 10 OF 48 MEDLINE
ACCESSION NUMBER: 1998042040 MEDLINE
DOCUMENT NUMBER: 98042040 PubMed ID: 9374627
TITLE: Regulation of tPA in endothelial cells exposed to cyclic strain: role of CRE, AP-2, and **SSRE** binding sites.
AUTHOR: Sumpio B E; Chang R; Xu W J; Wang X J; Du W
CORPORATE SOURCE: Department of Surgery (Vascular), Yale University School of Medicine, New Haven, Connecticut 06510, USA.
CONTRACT NUMBER: R01-HL-47345 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1997 Nov) 273 (5 Pt 1) C1441-8.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971217

AB We have previously reported that exposure of cultured bovine aortic endothelial cells (EC) to 10% average strain resulted in an increase in tissue plasminogen activator (tPA) mRNA, immunoreactive tPA protein, and tPA activity in the medium. The present study was designed to examine the regulation of tPA gene expression in EC by cyclic strain. We performed a functional analysis of the tPA promoter by transfecting bovine aortic EC with a 1.4-kilobase (kb) construct of the human tPA promoter coupled to chloramphenicol acetyltransferase. We found that subjecting the EC to 10% average strain (and not 6% average strain) resulted in a 2.6-fold increase in activity of the 1.4-kb tPA promoter by 4 h. Analysis of deletion mutants of the promoter transfected into EC demonstrated a 60% drop-off in activity between position -145 and -105. Deoxyribonuclease I protection analysis of the segment downstream of position -196 suggested involvement of activator protein-2 (AP-2) and adenosine 3',5'-cyclic monophosphate-responsive element (CRE)-like binding sites, which was confirmed by electrophoretic mobility shift assays. Site-directed mutants of either the AP-2 or CRE-like regions resulted in a 65% decrease in activity compared with the wild type. Double mutations abolished basal transcription and any strain-induced activity. A shear stress responsive element (**SSRE**) binding site is present at -945, but site-directed mutants did not show any drop in activity compared with wild type by cyclic strain. These studies demonstrate that cyclic strain regulates tPA gene transcription in bovine aortic EC and that this transcriptional activation is dependent on factors that are similar to those activated with phorbol ester.

L4 ANSWER 11 OF 48 MEDLINE
ACCESSION NUMBER: 1998012754 MEDLINE
DOCUMENT NUMBER: 98012754 PubMed ID: 9351401
TITLE: Egr-1 is activated in endothelial cells exposed to fluid shear stress and interacts with a novel **shear-stress-response element** in the PDGF A-chain promoter.
AUTHOR: Khachigian L M; Anderson K R; Halnon N J; Gimbrone M A Jr; Resnick N; Collins T
CORPORATE SOURCE: Department of Pathology, Brigham and Women's Hospital, Boston, MA 02115, USA.
CONTRACT NUMBER: HL 35716 (NHLBI)
HL-51150 (NHLBI)
PO1 HL-36028 (NHLBI)
SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (1997 Oct) 17 (10) 2280-6.
Journal code: 9505803. ISSN: 1079-5642.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971120

AB Exposure of vascular endothelial cells to fluid mechanical forces can modulate the expression of many genes involved in vascular physiology and pathophysiology. Here, we report that platelet-derived growth factor (PDGF) A-chain gene expression is induced at the level of transcription in cultured bovine aortic endothelial cells exposed to a physiologic level of

steady laminar shear stress (10 dyn/cm2). 5' Deletion analysis of the human PDGF-A promoter revealed that a GC-rich region near the TATA box was required for shear-inducible reporter gene expression. This element conferred shear inducibility onto a heterologous promoter-reporter construct that was otherwise unresponsive to shear stress. The induction of PDGF-A expression by shear was preceded by rapid and transient induction in the expression of the immediate-early gene, egr-1, which binds to GC-rich sequences. Gel shift studies indicated that shear-induced Egr-1 bound to the proximal PDGF-A promoter in a specific and time-dependent manner, displacing Sp1 from their overlapping recognition elements. Overlapping consensus binding sites for Egr-1 and Sp1 also appear in the proximal promoters of several other endothelial genes, including transforming growth factor-beta 1 and tissue factor, whose expression is modulated by shear stress. These findings define the Egr-1 binding site in the proximal PDGF-A promoter as a shear-stress-responsive element and suggest that shear-stimulated Egr-1 gene expression may be a unifying theme in the induction of various other endothelial genes exposed to biomechanical forces.

L4 ANSWER 12 OF 48 MEDLINE
ACCESSION NUMBER: 97471785 MEDLINE
DOCUMENT NUMBER: 97471785 PubMed ID: 9330726
TITLE: Endothelial gene regulation by laminar shear stress.
AUTHOR: Resnick N; Yahav H; Khachigian L M; Collins T; Anderson K R; Dewey F C; Gimbrone M A Jr
CORPORATE SOURCE: Department of Morphological Sciences, Bruce Rappaport Research Institute, Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel.
CONTRACT NUMBER: PO1-HL30628 (NHLBI)
SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1997) 430 155-64.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971119

AB Endothelial cells, because of their unique localization, are constantly exposed to fluid mechanical forces derived by the flowing blood. These forces, and more specifically shear stresses; affect endothelial structure and function, both in vivo and in vitro, and are implicated as contributing factors in the development of cardiovascular diseases. We have demonstrated earlier that the shear stress selectively induces the transcription of several endothelial genes, and have defined a **shear stress response element** (**SSRE**) in the promoter of platelet-derived-growth-factor B (PDGF-B), that is shared by additional endothelial shear stress responsive genes. Here we further characterize this **SSRE** and the nuclear factors that bind to it, and imply the possible role of the endothelium cytoskeleton in transducing shear stress, leading to the expression of PDGF-B/**SSRE** constructs in transfected endothelial cells exposed to shear stress. We also present, yet a new **shear stress response element** in the Platelet Derived Growth Factor A promoter, that contains a binding site to the transcription factors egr1/sp1. These results further demonstrate the complexity of gene regulation by hemodynamic forces, and support the important part that these forces have in the physiology and pathophysiology of the vessel wall.

L4 ANSWER 13 OF 48 MEDLINE
ACCESSION NUMBER: 96235743 MEDLINE
DOCUMENT NUMBER: 96235743 PubMed ID: 8666591
TITLE: Control of endothelial cell gene expression by flow.
AUTHOR: Malek A M; Izumo S
CORPORATE SOURCE: Department of Neurosurgery, Harvard Medical School, Boston,
MA 02215, USA.. ammalek@bics.bwh.harvard.edu
SOURCE: JOURNAL OF BIOMECHANICS, (1995 Dec) 28 (12) 1515-28.
Journal code: 0157375. ISSN: 0021-9290.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960819
Last Updated on STN: 19970203
Entered Medline: 19960806

AB The vessel wall is constantly subjected to, and affected by, the stresses resulting from the hemodynamic stimuli of transmural pressure and flow. At the interface between blood and the vessel wall, the endothelial cell plays a crucial role in controlling vessel structure and function in response to changes in hemodynamic conditions. Using bovine aortic endothelium monolayers, we show that fluid shear stress causes simultaneous differential regulation of endothelial-derived products. We also report that the downregulation of endothelin-1 mRNA by flow is a reversible process, and through the use of uncharged dextran supplementation demonstrate it to be shear stress- rather than shear rate-dependent. Recent work on the effect of fluid shear stress on endothelial cell gene expression of a number of potent endothelial products is reviewed, including vasoactive substances, autocrine and paracrine growth factors, thrombosis/fibrinolysis modulators, chemotactic factors, surface receptors and immediate-early genes. The encountered patterns of gene expression responses are classified into three categories: a transient increase with return to baseline (type I), a sustained increase (type II) and a biphasic response consisting of an early transient increase of varying extent followed by a pronounced and sustained decrease (type III). The importance of the dynamic character of the flow stimulus and the magnitude dependence of the response are presented. Potential molecular mechanisms of shear-induced gene regulation, including putative shear stress response elements (**SSRE**), are discussed. These results suggest exquisite modulation of endothelial cell phenotype by local fluid shear stress and may offer insight into the mechanism of flow-dependent vascular remodeling and the observed propensity of atherosclerosis formation around bifurcations and areas of low shear stress.

L4 ANSWER 14 OF 48 MEDLINE
ACCESSION NUMBER: 96222936 MEDLINE
DOCUMENT NUMBER: 96222936 PubMed ID: 8632623
TITLE: Flow-dependent regulation of gene expression in vascular endothelial cells.
AUTHOR: Ando J; Kamiya A
CORPORATE SOURCE: Department of Cardiovascular Biomechanics, Faculty of Medicine, University of Tokoyo, Tokyo, Japan.
SOURCE: JAPANESE HEART JOURNAL, (1996 Jan) 37 (1) 19-32. Ref: 40
Journal code: 0401175. ISSN: 0021-4868.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606

ENTRY DATE: Entered STN: 19960715
Last Updated on STN: 19970203
Entered Medline: 19960628

AB Vascular endothelial cells are constantly exposed to wall shear stress generated by blood flow. Endothelial cells act as mechanoceptors sensing and responding to shear stress, and play a role in flow-dependent phenomena such as angiogenesis, vascular remodeling and atherosclerosis. Numerous recent studies have demonstrated that endothelial cell functions change in response to shear stress, and that the responses are often accompanied by changes in related gene expression. More recently there has been evidence that genes known to be regulated by shear stress may have a common cis-element (shear stress responsive element; **SSRE**) in their promoter regions. A molecular mechanism for endothelial cell responses to mechanical stress is close to being elucidated. In this paper, shear-stress-mediated regulation of endothelial gene expression is reviewed.

L4 ANSWER 15 OF 48 MEDLINE
ACCESSION NUMBER: 95362821 MEDLINE
DOCUMENT NUMBER: 95362821 PubMed ID: 7635955
TITLE: Nuclear factor-kappa B interacts functionally with the platelet-derived growth factor B-chain **shear-stress response element** in vascular endothelial cells exposed to fluid shear stress.
AUTHOR: Khachigian L M; Resnick N; Gimbrone M A Jr; Collins T
CORPORATE SOURCE: Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: HL-35716 (NHLBI)
HL-51150 (NHLBI)
PO1 HL-36028 (NHLBI)
+
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1995 Aug) 96 (2) 1169-75.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950921
Last Updated on STN: 19970203
Entered Medline: 19950911

AB Hemodynamic forces, such as fluid shear stress, that act on the endothelial lining of the cardiovascular system can modulate the expression of an expanding number of genes crucial for homeostasis and the pathogenesis of vascular disease. A 6-bp core element (5'-GAGACC-3'), defined previously as a **shear-stress response element** is present in the promoters of many genes, including the PDGF B-chain, whose expression is modulated by shear stress. The identity of the nuclear protein(s) binding to this element has not yet been elucidated. Using electrophoretic mobility shift assays and in vitro DNase I footprinting, we demonstrate that nuclear factor-kappa B p50-p65 heterodimers, which accumulate in the nuclei of cultured vascular endothelial cells exposed to fluid shear stress, bind to the PDGF-B **shear-stress response element** in a specific manner. Mutation of this binding motif abrogated its interaction with p50-p65 and abolished the ability of the promoter to mediate increased gene expression in endothelial cells exposed to shear stress. Transient cotransfection studies indicate that p50-p65 is able to activate PDGF-B **shear-stress response element** -dependent reporter gene expression in these cells. These findings thus implicate nuclear factor-kappa B in the transactivation of an endothelial

gene responding to a defined fluid mechanical force.

L4 ANSWER 16 OF 48 MEDLINE
ACCESSION NUMBER: 95340059 MEDLINE
DOCUMENT NUMBER: 95340059 PubMed ID: 7615157
TITLE: Hemodynamic forces are complex regulators of endothelial gene expression.
AUTHOR: Resnick N; Gimbrone M A Jr
CORPORATE SOURCE: Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115-5817, USA.
CONTRACT NUMBER: P01-HL30628 (NHLBI)
R37-HL51150 (NHLBI)
SOURCE: FASEB JOURNAL, (1995 Jul) 9 (10) 874-82. Ref: 55
Journal code: 8804484. ISSN: 0892-6638.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950905
Last Updated on STN: 19970203
Entered Medline: 19950824

AB Vascular endothelial cells, by virtue of their unique anatomical position,
are constantly exposed to the fluid mechanical forces generated by flowing
blood. In vitro studies with model flow systems have demonstrated that wall shear stresses can modulate various aspects of endothelial structure and function. Certain of these effects appear to result from the regulation of expression of endothelial genes at the transcriptional level. Recent molecular biological studies have defined a **"shear stress response element"** (**SSRE**) in
the promoter of the human platelet-derived growth factor (PDGF)-B chain gene that interacts with DNA binding proteins in the nuclei of shear-stressed endothelial cells to up-regulate transcriptional activity. Insertion of this element into reporter genes also renders them shear-inducible. Further characterization of this and other positive (and negative) shear-responsive genetic regulatory elements, as well as their transactivating factors, should enhance our understanding of vascular endothelium as an integrator of humoral and biomechanical stimuli in health and disease.

L4 ANSWER 17 OF 48 MEDLINE
ACCESSION NUMBER: 94314998 MEDLINE
DOCUMENT NUMBER: 94314998 PubMed ID: 7518844
TITLE: Shear stress selectively upregulates intercellular adhesion
molecule-1 expression in cultured human vascular endothelial cells.
AUTHOR: Nagel T; Resnick N; Atkinson W J; Dewey C F Jr; Gimbrone M A Jr
CORPORATE SOURCE: Harvard-Massachusetts Institute of Technology, Division of Health Sciences and Technology, Cambridge, Massachusetts 02139.
CONTRACT NUMBER: P01-HL36028 (NHLBI)
P01-HL48743 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1994 Aug) 94 (2) 885-91.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Space

Life Sciences
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940905
Last Updated on STN: 19970203
Entered Medline: 19940825

AB Hemodynamic forces induce various functional changes in vascular endothelium, many of which reflect alterations in gene expression. We have recently identified a cis-acting transcriptional regulatory element, the **shear stress response element** (**SSRE**), present in the promoters of several genes, that may represent a common pathway by which biomechanical forces influence gene expression. In this study, we have examined the effect of shear stress on endothelial expression of three adhesion molecules: intercellular adhesion molecule-1 (ICAM-1), which contains the **SSRE** in its promoter, and E-selectin (ELAM-1) and vascular cell adhesion molecule-1 (VCAM-1), both of which lack the **SSRE**. Cultured human umbilical vein endothelial cells, subjected to a physiologically relevant range of laminar shear stresses (2.5-46 dyn/cm2) in a cone and plate apparatus for up to 48 h, showed time-dependent but force-independent increases in surface immunoreactive ICAM-1. Upregulated ICAM-1 expression was correlated with increased adhesion of the JY lymphocytic cell line. Northern blot analysis revealed increased ICAM-1 transcript as early as 2 h after the onset of shear stress. In contrast, E-selectin and vascular cell adhesion molecule-1 transcript and cell-surface protein were not upregulated at any time point examined. This selective regulation of adhesion molecule expression in vascular endothelium suggests that biomechanical forces, in addition to humoral stimuli, may contribute to differential endothelial gene expression and thus represent pathophysiologically relevant stimuli in inflammation and atherosclerosis.

L4 ANSWER 18 OF 48 MEDLINE
ACCESSION NUMBER: 94245207 MEDLINE
DOCUMENT NUMBER: 94245207 PubMed ID: 7514568
TITLE: Isolation and chromosomal localization of the human endothelial nitric oxide synthase (NOS3) gene.
AUTHOR: Robinson L J; Weremowicz S; Morton C C; Michel T
CORPORATE SOURCE: Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115.
SOURCE: GENOMICS, (1994 Jan 15) 19 (2) 350-7.
Journal code: 8800135. ISSN: 0888-7543.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940629
Last Updated on STN: 19960129
Entered Medline: 19940620

AB Nitric oxide (NO) is an important intercellular signaling molecule synthesized in diverse human tissues by proteins encoded by a family of NO synthase (NOS) genes. The similarity of sequence and cofactor binding sites has suggested that the NOS genes may also be related to cytochrome P450 reductase, as well as to plant and bacterial oxidoreductases. Endothelial NOS activity is a major determinant of vascular tone and blood pressure, and in several important (and sometimes hereditary) disease states, such as hypertension, diabetes, and atherosclerosis, the endothelial NO signaling system appears to be abnormal. To explore the relationship of the endothelial NOS gene to other similar genes, and to delineate the genetic factors involved in regulating endothelial NOS activity, we isolated the human gene encoding the endothelial NOS. Genomic

clones containing the 5' end of this gene were identified in a human genomic library by applying a polymerase chain reaction (PCR)-based approach. Identification of the human gene for endothelial NOS (NOS3) was confirmed by nucleotide sequence analysis of the first coding exon, which was found to be identical to its cognate cDNA. The NOS3 gene spans at least 20 kb and appears to contain multiple introns. The transcription start site and promoter region of the NOS3 gene were identified by primer extension and ribonuclease protection assays. Sequencing of the putative promoter revealed consensus sequences for the **shear stress-response element**, as well as cytokine-responsive cis regulatory sequences, both possibly important to the roles played by NOS3 in the normal and the diseased cardiovascular system.(ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 19 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:283845 CAPLUS
TITLE: The eukaryotic two-component histidine kinase Sln1p regulates OCH1 via the transcription factor, Skn7p
AUTHOR(S): Li, Sheng; Dean, Susan; Li, Zhijian; Horecka, Joe; Deschenes, Robert J.; Fassler, Jan S.
CORPORATE SOURCE: Department of Biological Sciences, University of Iowa, Iowa City, IA, 52242, USA
SOURCE: Molecular Biology of the Cell (2002), 13(2), 412-424
CODEN: MBCEEV; ISSN: 1059-1524
PUBLISHER: American Society for Cell Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The yeast "two-component" osmotic stress phosphorelay consists of the histidine kinase, Sln1p, the phosphorelay intermediate, Ypd1p and two response regulators, Ssk1p and Skn7p, whose activities are regulated by phosphorylation of a conserved aspartyl residue in the receiver domain. Dephospho-Ssk1p leads to activation of the hyper-osmotic response (HOG) pathway, whereas phospho-Skn7p presumably leads to activation of hypo-osmotic response genes. The multifunctional Skn7 protein is important in oxidative as well as osmotic stress; however, the Skn7p receiver domain aspartate that is the phosphoacceptor in the SLN1 pathway is dispensable for oxidative stress. Like many well-characterized bacterial response regulators, Skn7p is a transcription factor. In this report we investigate the role of Skn7p in osmotic response gene activation. Our studies reveal that the Skn7p HSF-like DNA binding domain interacts with a cis-acting element identified upstream of OCH1 that is distinct from the previously defined HSE-like Skn7p binding site. Our data support a model in which Skn7p receiver domain phosphorylation affects transcriptional activation rather than DNA binding to this class of DNA binding site.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:927215 CAPLUS
DOCUMENT NUMBER: 136:65287
TITLE: Promoter sequence of rice phytosulfokine (PSK) gene and its use of enhancement of gene expression in transgenic plants
INVENTOR(S): Sakagami, Yoji; Yang, He Ping; Matsubayashi, Yoshikatsu
PATENT ASSIGNEE(S): Nagoya University, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 20 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001352981	A2	20011225	JP 2000-179826	20000615
EP 1172441	A1	20020116	EP 2001-113542	20010612
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002103363	A1	20020801	US 2001-880006	20010614

PRIORITY APPLN. INFO.: JP 2000-179826 A 20000615

AB This invention provides a sequence of promoter fo phytosulfokine (PSK) gene cloned from rice. The promoter region comprises of one CAAT box, two CCAAT boxes, three **SSRE** element, one enhance and three E boxes. The PSK promoter is 3359 bp long and the promoter deletion expt. showed that the fragment (-1911 - -1) was most active in regulation of reporter gene expression. The PSK promoter can be used for enhancement of gene expression in transgenic plants.

L4 ANSWER 21 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:457190 CAPLUS
DOCUMENT NUMBER: 133:85122
TITLE: Expression vectors comprising multiple shear stress responsive elements (**SSRE**) and a gene of interest and modulating vasculogenesis and/or angiogenesis
INVENTOR(S): Resnick, Nitzan
PATENT ASSIGNEE(S): Florence Medical Ltd., Israel
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039275	A2	20000706	WO 1999-IL702	19991223
WO 2000039275	A3	20001026		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6440726	B1	20020827	US 1998-220510	19981224
AU 2000017954	A5	20000731	AU 2000-17954	19991223
EP 1141266	A2	20011010	EP 1999-961261	19991223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:
US 1998-113863P P 19981224
US 1998-220510 A 19981224
US 1998-220510P P 19981224
WO 1999-IL702 W 19991223

AB This invention provides expression vectors comprising multiple shear stress responsive elements (**SSRE**) and one or more genes of interest and methods of treating disorders related to or assocd. with vasculogenesis and/or angiogenesis conditions.

L4 ANSWER 22 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:194533 CAPLUS
DOCUMENT NUMBER: 132:345853
TITLE: Unidirectional and Oscillatory Shear Stress

Differentially Modulate NOS III Gene Expression
AUTHOR(S): Si[redacted]i, P.; Formentin, K.; Bouzoure[redacted] K.; Daniel, F.; Brunner, H. R.; Hayoz, D.
CORPORATE SOURCE: Division of Hypertension and Vascular Medicine, CHUV, Lausanne, 1011, Switz.
SOURCE: Nitric Oxide (2000), 4(1), 47-56
CODEN: NIOXF5; ISSN: 1089-8603
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Atherosclerotic plaques preferentially develop in regions exposed to a low mean shear stress and cyclic reversal of flow direction (oscillatory flow). This contrasts with plaque-free zones where endothelial cells are exposed to unidirectional flow. Previous works from our lab. using a unique exptl. flow system demonstrated the existence of a differential regulation of endothelial nitric oxide synthase (NOS III) gene expression by unidirectional and oscillatory flow patterns. We further studied the possible mechanisms responsible for selective unresponsiveness of NOS III gene regulation to oscillatory flow. The results obtained demonstrate that (i) induction of the activity of the 1600-base-pair NOS III gene promoter by unidirectional and oscillatory shear stress is modulated by similar mechanisms that involve NF-.kappa.B activation, but do not involve Ras-dependent MAP kinase activation, and (ii) the lack of induction of NOS III gene regulation by oscillatory shear stress can be attributed to the activation of a yet unidentified neg. cis-acting element present in the NOS III gene. (c) 2000 Academic Press.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:101186 CAPLUS
DOCUMENT NUMBER: 133:41452
TITLE: Role of LOX-1, an endothelial oxidized low-density lipoprotein receptor, in vascular disorders
AUTHOR(S): Nagase, Miki; Ando, Katsuyuki; Fujita, Toshiro
CORPORATE SOURCE: Department of Internal Medicine, University of Tokyo School of Medicine, Tokyo, 112-8688, Japan
SOURCE: International Congress Series (1999), 1181(Common Disease: Genetic and Pathogenetic Aspects of Multifactorial Diseases), 227-236
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LOX-1 is a novel endothelial receptor for oxidized low-d. lipoprotein (OxLDL). Its biol. roles have not yet been clarified. In the present study we performed rat LOX-1 cDNA and genomic DNA cloning and examd. the regulation of its expression using in vitro and in vivo systems. Cloning was performed by screening the cDNA and genomic DNA library. Transcription initiation site was detd. by primer extension and S1 mapping. Gene expression was examd. by Northern blotting. The rat LOX-1 cDNA encoded 364 amino acids consisting of N-terminal cytoplasmic, single-transmembrane, triple repeats, and C-type lectin-like domains. The LOX-1 gene was encoded by eight exons. The promoter region contained AP-1, AP-2, NF-.kappa.B binding sites, and a **shear stress response element**. LOX-1 mRNA in cultured vascular endothelial cells was markedly increased by mech. stress, lysophosphatidylcholine, advanced glycation end products, and TNF-.alpha.. LOX-1 expression was also markedly upregulated in the vasculature of hypertensive rats. LOX-1 expression was modulated by

stimuli related to major risk factors for atherosclerotic cardiovascular diseases, implicating a pivotal role for OxLDL/LOX-1 in the development of atherosclerotic vascular complications.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:653134 CAPLUS
DOCUMENT NUMBER: 132:91117
TITLE: Endothelial gene regulation by fluid shear forces
AUTHOR(S): Resnick, Nitzan; Wolfovitz, Efrat; Zilberstein, Shachar
CORPORATE SOURCE: Department of Anatomy and Cell Biology, Bruce Rappaport Medical Research, The Rappaport Faculty of Medicine - Technion, Haifa, 31096, Israel
SOURCE: Endothelial Cell Research Series (1999), 6(Mechanical Forces and the Endothelium), 127-147
CODEN: ECRSFY; ISSN: 1384-1270
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 92 refs. The remodeling of Blood vessels accompanies physiol. and pathol. processes such as, angiogenesis and vasculogenesis, atherosclerosis, hypertension and restenosis. Vessel remodeling occurs in response to both biochem. and biomech. stimuli, and has been shown to be dependent on the presence of an intact endothelial layer. By virtue of their anatomical position, endothelial cells are constantly exposed to hemodynamic forces generated by the flowing blood, forces that consists of fluid shear stress, cyclic strain and pressure. These forces affect endothelial cells structure and function, changes that are often mediated by the induction or shut-off of endothelial genes. Up to date few dozens endothelial genes have been found to be regulated by hemodynamic forces. Promoter anal. of some of the genes resulted in the definition of pos. and neg. cis-acting elements that are essential for their responsiveness to biomech. forces. These shear stress response elements (SSREs) bind transcription factors, among them, NF.kappa.B, NFATc2, Sp1, Egr1, Fos and Jun, that are activated themselves by hemodynamic forces. This review attempts to summarize the effects of hemodynamic forces, and more specifically fluid shear stress, on endothelial gene regulation in vitro and in vivo and point to several SSREs and transcription factors that are involved in this regulation. New technologies, as well as, new in vitro shear stress models facilitating the study of endothelial gene regulation by shear stress will be discussed. Finally, special attention will be given to results accumulating from recent studies on the regulation of endothelial genes by complex (pathol.) shear stresses. Vascular remodeling is the sum of multiple events, some of which are regulated by biomech. forces, and mediated by the regulation of vascular endothelial genes. It is thus hoped that unraveling the complexity of endothelial gene regulation by biomech. forces contributes to our understanding of the physiol. processes in the circulatory system and the pathogenesis of vascular diseases.
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:653133 CAPLUS
DOCUMENT NUMBER: 132:91116

TITLE: Flow-induced endothelial gene regulation
AUTHOR(S): And[redacted] Joji; Korenaga, Risa; Kamiya, [redacted]ra
CORPORATE SOURCE: Department of Biomedical Engineering, Graduate School of Medicine, University of Tokyo, Tokyo, 113, Japan
SOURCE: Endothelial Cell Research Series (1999), 6(Mechanical Forces and the Endothelium), 111-126
CODEN: ECRSFY; ISSN: 1384-1270
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 42 refs. Shear stress generated by blood flow can modulate both the morphol. and functions of vascular endothelial cells. In most cases, gene expression assocd. with endothelial function is also altered by shear stress. To date, the expression of nearly twenty endothelial genes has been shown to be up-and/or down-regulated by shear stress, and several related transcription factors and cis-acting shear-stress-response elements have been identified. We recently characterized a neg. **shear-stress-response element** in the murine vascular adhesion mol.-1 (VCAM-1) gene. Exposure of mouse venule endothelial cells to shear stress decreased VCAM-1 protein cell surface expression and inhibited adhesion to lymphocytes. The decrease in protein expression was due to a decrease in VCAM-1 mRNA levels, which resulted from the suppression of VCAM-1 gene transcription induced by shear stress.

A double AP-1 binding site in the VCAM-1 gene promoter was found to function as a cis-element for this neg. transcriptional regulation. To det. the no. of endothelial genes responsive to shear stress, differential display of endothelial mRNAs was performed. In cells exposed to a shear stress of 15 dynes/cm2 for 6h, approx. 4% of the mRNA species increased more than two-fold or decreased to less than half the levels in static control cells. Thus, it seems that a large no. of known or unknown shear-response genes are involved in blood flow-dependent phenomena including angiogenesis, vascular remodeling, and atherosclerosis.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:395456 CAPLUS
DOCUMENT NUMBER: 131:197968
TITLE: Enhanced expression of LOX-1, an oxidized low-density lipoprotein receptor, in the kidney of salt-sensitive hypertensive rats
AUTHOR(S): Nagase, Miki; Kaname, Shinya; Ando, Katsuyuki; Fujita, Toshiro
CORPORATE SOURCE: Department of Nephrology and Endocrinology, University of Tokyo School of Medicine, Japan
SOURCE: Therapeutic Research (1999), 20(5), 1340-1344
CODEN: THREEL; ISSN: 0289-8020
PUBLISHER: Raifu Saiensu Shuppan K.K.
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Lox-1 is a recently-identified endothelial receptor for oxidized low-d. lipoprotein. In the present study, the authors detd. the structure of tat LOX-1 cDNA and genomic DNA. LOX-1 cDNA encoded a protein of 364 amino acids consisting of N-terminal cytoplasmic, single transmembrane, extracellular three repeats of a 46-amino-acid motif and C-type lectin-like domains. The 3'-untranslated region contained seven A+U-rich elements for rapid degrdn. of mRNA. Two isoforms of mRNA were generated

by alternative use of two polyadenylation signals. The rat LOX-1 gene was encoded by a single copy gene spanning over 19 kilobases and consisted of eight exons. Exon boundaries correlated well with the functional domain boundaries of the receptor protein. The promoter region contained multiple cis-elements such as NF-.kappa.B, AP-1, AP-2 sites, and a **shear-stress response element.** LOX-1 expression was markedly upregulated by mech. stress and cytokines in cultured vascular endothelial cell. LOX-1 expression was also enhanced in the aorta and kidney of hypertensive rats. These data suggest a role for LOX-1 in the pathophysiol. of hypertensive target organ complication.

L4 ANSWER 27 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:539097 CAPLUS
DOCUMENT NUMBER: 129:300613
TITLE: Vascular endothelium, hemodynamic forces and atherogenesis
AUTHOR(S): Gimbrone, Michael A., Jr.; Topper, James N.
CORPORATE SOURCE: Vascular Research Division, Departments of Pathology, Harvard Medical School, Boston, MA, USA
SOURCE: International Congress Series (1998), 1155(Atherosclerosis XI), 949-955
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 22 refs. The localization of atherosclerotic lesions to arterial geometries assocd. with disturbed flow patterns suggests an important role for local hemodynamic forces in atherogenesis. There is increasing evidence that the vascular endothelium, which is directly exposed to fluid mech. forces generated by blood flow, can discriminate among these stimuli and transduce them into genetic regulatory events. At the level of individual genes, this regulation is accomplished via the interaction of various transcription factors, such as NF-.kappa.B and Egr-1, with "shear-stress response elements" or SSREs, such as the GAGACC motif in the proximal promoter of the human PDGF-B gene, or the Egr-1/Sp1-binding sites in the PDGF-A gene. At the level of multiple genes, distinct patterns of up- and downregulation appear to be elicited by exposure to steady laminar shear stresses vs. comparable levels of nonlaminar (e.g., turbulent) shear stresses or cytokine stimulation (e.g., IL-1.beta.). Certain genes that are upregulated by a steady laminar shear-stress stimulus (such as ecNOS, COX-2 and Mn-SOD) support "vasoprotective" (anti-inflammatory, antithrombotic, antioxidant) functions in the endothelium. The selective and sustained expression of these and related "antiatherogenic genes" in the endothelial lining of lesion-protected areas represent a mechanism whereby hemodynamic forces can influence lesion formation and progression.

L4 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:376479 CAPLUS
DOCUMENT NUMBER: 127:91159
TITLE: Characterization and sequence of an additional 15-lipoxygenase transcript and of the human gene
AUTHOR(S): Kritzik, Marcie R.; Ziober, Amy F.; Dicharry, Sherry; Conrad, Douglas J.; Sigal, Elliott
CORPORATE SOURCE: Institute of Biochemistry and Cell Biology, Syntex Discovery Research, Palo Alto, USA
SOURCE: Biochimica et Biophysica Acta (1997), 1352(3), 267-281
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal

LANGUAGE: English

AB 15-Lipoxygenase is a l[redacted]d-peroxidating enzyme that oxi es fatty acids, such as those esterified to cellular membranes. It has been implicated in the oxidative modification of low-d. lipoprotein and is thus thought to contribute to the development of atherosclerosis. The enzyme has also been shown to be specifically induced by interleukin-4 in human blood monocytes. Two 15-lipoxygenase-hybridizing messages were detected in these cells; one (2.7 kb) corresponds to the previously isolated cDNA for 15-lipoxygenase, while the other (4 kb) was of unknown origin. We have isolated and characterized this 4 kb transcript. Our expts. show that it has 1.2 kb addnl. sequence in its 3' untranslated region, and that it is generated from genomic sequences through differential polyA site selection. We present studies to address the functional significance of the extended 3'UTR. Selection of an upstream polyadenylation signal results in prodn. of the 2.7 kb transcript. In addn., we present here for the first time the cloning and sequence of the human 15-lipoxygenase gene, as well as the identification of regulatory elements in the promoter region of this gene.

L4 ANSWER 29 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:38558 CAPLUS
DOCUMENT NUMBER: 124:113149
TITLE: Blood flow modulates vascular endothelial gene expressions
AUTHOR(S): Ando, Joji
CORPORATE SOURCE: Fac. Med., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Tanpakushitsu Kakusan Koso (1996), 41(1), 26-33
CODEN: TAKKAJ; ISSN: 0039-9450
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review, with 23 refs., on effect of wall shear stress (SS) by blood flow on expression of VCAM-1 mRNA on endothelial cells, other genes modulated by blood flow, and discovery of **SSRE** (SS response element).

L4 ANSWER 30 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:831146 CAPLUS
DOCUMENT NUMBER: 123:308114
TITLE: Endothelial gene regulation by biomechanical forces
AUTHOR(S): Resnick, Nitzan; Bauer, Sumpio E.; Du, Wei; Gimbrone, Michael A. Jr.
CORPORATE SOURCE: Department Pathology, Brigham and Women's Hospital, Boston, MA, 02115-5817, USA
SOURCE: International Congress Series (1995), 1066(Atherosclerosis X), 838-43
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hemodynamic forces generated by the pulsatile flow of blood through the circulatory system have been shown to influence the structure and function of vascular endothelium. Several groups, using in vitro systems, have demonstrated that defined biomech. forces, including wall shear stress and cyclic strain, can modulate endothelial gene expression. In particular, our group has demonstrated that PDGF B-chain gene transcription is induced by exposure of cultured endothelial cells to a physiol. level of laminar shear stress. We have defined a region within the PDGF B-chain promoter that is responsible for this shear-induced gene expression, and have called this the **"Shear Stress Response Element"** (**SSRE**). This promoter element binds nuclear

proteins extd. from shear-stressed endothelial cells. [redacted]core sequence (GAGACC) within the **SS**[redacted] is also present in the promote[redacted] of several other endothelial genes that are responsive to shear stress. This core sequence was shown by electromobility shift assays to be a nuclear-protein binding site. Moreover, hybrid promoters contg. the **SSRE** sequence (as present in the PDGF B-chain promoter) were inducible by shear stress when transfected into bovine aortic endothelial cells, thus confirming that this element is both necessary and sufficient for gene induction by laminar shear stress. We have recently extended these studies to another physiol. relevant hemodynamic force, cyclic strain, induced by biaxial stretching. Interestingly, the **SSRE** binds to nuclear proteins extd. from endothelial cells, but not from smooth muscle cells, exposed to the same level of cyclic strain (10% av. strain, 60 cycles/min). These results suggest that different biomech. forces may act on the endothelium through a common, but cell-type-specific, mechanism to activate gene transcription.

L4 ANSWER 31 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:402274 CAPLUS
DOCUMENT NUMBER: 121:2274
TITLE: Promoter analysis of human inducible nitric oxide synthase gene associated with cardiovascular homeostasis
AUTHOR(S): Nunokawa, Youichi; Ishida, Nobuhiro; Tanaka, Shoji
CORPORATE SOURCE: Suntory Inst. Biomed. Res., Osaka, 618, Japan
SOURCE: Biochemical and Biophysical Research Communications (1994), 200(2), 802-7
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors previously showed that interferon (IFN)-.gamma. inhibited the proliferation of rat vascular smooth muscle cells (VSMC) by generation of nitric oxide (NO) through the induction of an NO synthase (NOS) and cloned the rat inducible NOS cDNA in VSMC (VSM-NOS). To study the regulation of human inducible NOS (HiNOS) transcription in VSMC, the authors now cloned and sequenced a 2.9-kb fragment for the hiNOS gene contg. a putative promoter, exon 1 and exon 2. The 5'-flanking region contains several consensus sequences for the binding of transcription factors involved in the inducibility of other genes by cytokines. These include IFN-.gamma. responsive element and NF-IL6 and NF-.kappa.B binding consensus sequences. Interestingly, the hiNOS gene contains a shear-stress responsive element (GAGACC) which was also found to exist in humans endothelial-type NOS but not in murine inducible NOS.

L4 ANSWER 32 OF 48 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:642858 CAPLUS
DOCUMENT NUMBER: 119:242858
TITLE: Platelet-derived growth factor B chain promoter contains a cis-acting fluid shear-stress-responsive element. [Erratum to document cited in CA119(5):42657a]
AUTHOR(S): Resnick, Nitzan; Collins, Tucker; Atkinson, William; Bonthron, David T.; Dewey, C. Forbes, Jr.; Gimbrone, Michael A., Jr.
CORPORATE SOURCE: Harvard Med. Sch., Brigham and Women's Hosp., Boston, MA, 02115, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(16), 7908
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The errors were not reflected in the abstr. or the index entries.

L4 ANSWER 33 OF 48 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:442657 CAPLUS
DOCUMENT NUMBER: 11[redacted]2657
TITLE: Platelet-derived growth factor B chain promoter contains a cis-acting fluid shear-stress-responsive element
AUTHOR(S): Resnick, Nitzan; Collins, Tucker; Atkinson, William; Bonthron, David T.; Dewey, C. Forbes, Jr.; Gimbrone, Michael A., Jr.
CORPORATE SOURCE: Harvard Med. Sch., Brigham and Women's Hosp., Boston, MA, 02115, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(10), 4591-5
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The B chain of platelet-derived growth factor (PDGF-B) was used as a model to investigate the mechanisms of shear-stress-induced gene regulation in cultured bovine aortic endothelial cells (BAECs). Northern blot anal. revealed elevated endogenous PDGF-B transcript levels in BAECs, after exposure to a physiol. level of laminar shear stress (10 dynes/cm2; 1 dyne = 100 mN) for 4 h. A transfected reporter gene, consisting of a 1.3-kb fragment of the human PDGF-B promoter coupled to chloramphenicol acetyltransferase (CAT), indicated a direct effect on transcriptional activity. Transfection of a series of PDGF-B-CAT deletion mutants led to the characterization of a cis-acting component within the PDGF-B promoter that was necessary for shear-stress responsiveness. In gel-shift assays, overlapping oligonucleotide probes of this region formed several protein-DNA complexes with nuclear exts. prepd. from both static and shear-stressed BAECs. A 12-bp component (CTCTCAGAGACC) was identified that formed a distinct pattern of complexes with nuclear proteins extd. from shear-stressed BAECs. This shear-stress-responsive element does not encode binding sites for any known transcription factor but does contain a core binding sequence (GAGACC), as defined by deletion mutation in gel-shift assays. Interestingly, this putative transcription factor binding site is also present in the promoters of certain other endothelial genes, including tissue plasminogen activator, intercellular adhesion mol. 1, and transforming growth factor .beta.1, that also are induced by shear stress. Thus, the expression of PDGF-B and other pathophysiol. relevant genes in vascular endothelium appears to be regulated, in part, by shear-stress-induced transcription factors interacting with a common promoter element.

L4 ANSWER 34 OF 48 USPATFULL
ACCESSION NUMBER: 2002:217074 USPATFULL
TITLE: Expression vectors comprising multiple shear stress responsive elements (**SSRE**) and methods of use for treating disorders related to vasculogenesis and/or angiogenesis in a shear stress environment
INVENTOR(S): Resnick, Nitzan, Haifa, ISRAEL
PATENT ASSIGNEE(S): Florence Medical, Ltd., Kfar Saba, ISRAEL (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6440726	B1	20020827
APPLICATION INFO.:	US 1998-220510		19981224 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Nguyen, Dave T.
LEGAL REPRESENTATIVE: Nath & Associates PLLC, Novick, Harold L., Juneau, Todd

L.
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 1883
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides expression vectors comprising multiple shear stress responsive elements and methods of treating disorders related to or associated with vasculogenesis and/or angiogenesis in the vasculature.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 35 OF 48 USPATFULL
ACCESSION NUMBER: 2002:192289 USPATFULL
TITLE: Promoter derived from phytosulfokine precursor gene
INVENTOR(S): Sakagami, Yoji, Nagoya City, JAPAN
Yang, Heping, Nagoya City, JAPAN
Matsubayashi, Yoshikatsu, Nagoya City, JAPAN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002103363	A1	20020801	
APPLICATION INFO.:	US 2001-880006	A1	20010614	(9)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2000-179826	20000615

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Robert G. Mukai, BURNS, DOANE, SWECKER & MATHIS, L.L.P., P.O. Box 1404, Alexandria, VA, 22313-1404
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 1258
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a novel promoter derived from gene of phytosulfokine precursor derived from rice. The novel promoter of this invention can enhance expression of an exogenous structural gene with higher potency compared with conventional cauliflower mozaic virus 35S promoter

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 36 OF 48 USPATFULL
ACCESSION NUMBER: 2002:157674 USPATFULL
TITLE: UPREGULATION OF TYPE III ENDOTHELIAL CELL NITRIC OXIDE SYNTHASE BY AGENTS THAT DISRUPT ACTIN CYTOSKELETAL ORGANIZATION
INVENTOR(S): LIAO, JAMES K., WESTON, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002082281	A1	20020627	
	US 6423751	B2	20020723	
APPLICATION INFO.:	US 1998-115387	A1	19980714	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: EDWARD R GATES, WOLF GREENFIELD & SACKS, 600 ATLANNTIC AVENUE, BOSTON, MA, 02210
NUMBER OF CLAIMS: 77
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 2598
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A use for agents that disrupt actin cytoskeletal organization is provided. In the instant invention, agents that disrupt actin cytoskeletal organization are found to upregulate endothelial cell Nitric Oxide Synthase activity. As a result, agents that disrupt actin cytoskeletal organization are useful in treating or preventing conditions that result from the abnormally low expression and/or activity of endothelial cell Nitric Oxide Synthase. Such conditions include pulmonary hypertension, ischemic stroke, impotence, heart failure, hypoxia-induced conditions, insulin deficiency, progressive renal disease, gastric or esophageal motility syndrome, etc. Subjects thought to benefit mostly from such treatments include nonhyperlipidemics and nonhypercholesterolemics, but not necessarily exclude hyperlipidemics and hypercholesterolemics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 37 OF 48 USPATFULL

ACCESSION NUMBER:	2001:14453 USPATFULL
TITLE:	Upregulation of Type III endothelial cell nitric oxide synthase by rho GTPase function inhibitors
INVENTOR(S):	Liao, James K., Weston, MA, United States
PATENT ASSIGNEE(S):	Brigham and Women's Hospital, Inc., Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6180597	B1	20010130
APPLICATION INFO.:	US 1998-132849		19980811 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1998-92618, filed on 5 Jun 1998, now abandoned		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-78774P	19980319 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Russell, Jeffrey E.
LEGAL REPRESENTATIVE:	Wolf, Greenfield & Sacks, P.C.
NUMBER OF CLAIMS:	93
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	27 Drawing Figure(s); 16 Drawing Page(s)
LINE COUNT:	2725

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A use for rho GTPase function inhibitors is provided. In the instant invention, rho GTPase function inhibitors are found to upregulate endothelial cell Nitric Oxide Synthase activity. As a result, rho GTPase function inhibitors are useful in treating or preventing conditions that result from the abnormally low expression and/or activity of endothelial cell Nitric Oxide Synthase. Such conditions include pulmonary hypertension, ischemic stroke, impotence, heart failure, hypoxia-induced conditions, insulin deficiency, progressive renal disease, gastric or esophageal motility syndrome, etc. Subjects thought to benefit mostly from such treatments include nonhyperlipidemics and nonhypercholesterolemics, but do not necessarily exclude hyperlipidemics and hypercholesterolemics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 38 OF 48 USPATFULL

ACCESSION NUMBER:	2001:4462 USPATFULL
TITLE:	Methods for the diagnosis, prognosis and treatment of

glaucoma and related disorders
INVENTOR(S): Ngu[redacted], Thai D., Mill Valley, CA, United States
Polansky, Jon R., Mill Valley, CA, United States
Chen, Pu, Rohnert Park, CA, United States
Chen, Hua, San Francisco, CA, United States
PATENT ASSIGNEE(S): The Regents of the University of California, Oakland, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6171788	B1	20010109
APPLICATION INFO.:	US 1997-938669		19970926 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1997-791154, filed on 28 Jan 1997, now abandoned
DOCUMENT TYPE: Patent
FILE SEGMENT: Granted
PRIMARY EXAMINER: Schwartzman, Robert A.
ASSISTANT EXAMINER: Shibuya, Mark L.
LEGAL REPRESENTATIVE: Howrey, Simon, Arnold & White, LLP
NUMBER OF CLAIMS: 49
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 21 Drawing Figure(s); 23 Drawing Page(s)
LINE COUNT: 2803
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The nucleic acid upstream of the TIGR protein encoding sequence can be used to diagnose glaucoma. Polymorphisms, base substitutions, base additions located with the upstream and within TIGR exons can also be used to diagnose glaucoma. In addition, polymorphisms, base substitutions, base additions located with the upstream and within TIGR exons can also be used to prognose glaucoma.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 39 OF 48 USPATFULL
ACCESSION NUMBER: 2000:153742 USPATFULL
TITLE: Upregulation of Type III endothelial cell Nitric Oxide Synthase by HMG-CoA reductase inhibitors
INVENTOR(S): Liao, James K., Weston, MA, United States
Laufs, Ulrich, Cologne, Germany, Federal Republic of
Endres, Matthias, Berlin, Germany, Federal Republic of
Moskowitz, Michael A., Belmont, MA, United States
PATENT ASSIGNEE(S): The General Hospital Corporation, Boston, MA, United States (U.S. corporation)
The Brigham and Women's Hospital Inc., Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6147109		20001114
APPLICATION INFO.:	US 1998-132848		19980811 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-62093P	19971014 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Jordan, Kimberly
LEGAL REPRESENTATIVE: Wolf, Greenfield & Sacks, P.C.
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 1864
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A new use for HMG-CoA reductase inhibitors is provided. In the instant invention, HMG-CoA reductase inhibitors are found to upregulate endothelial cell Nitric Oxide Synthase activity through a mechanism

other than preventing the formation of oxidative-LDL. As a result, HMG-CoA reductase inhibitors are useful in treating or preventing conditions that result from the abnormally low expression and/or activity of endothelial cell Nitric Oxide Synthase. Such conditions include pulmonary hypertension, ischemic stroke, impotence, heart failure, hypoxia-induced conditions, insulin deficiency, progressive renal disease, gastric or esophageal motility syndrome, etc. Subjects thought to benefit mostly from such treatments include nonhyperlipidemics and nonhypercholesterolemics, but not necessarily exclude hyperlipidemics and hypercholesterolemics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 40 OF 48 USPATFULL

ACCESSION NUMBER:	77:1452 USPATFULL
TITLE:	Charge transfer device
INVENTOR(S):	Sangster, Frederik Leonard Johan, Eindhoven, Netherlands
PATENT ASSIGNEE(S):	U.S. Philips Corporation, New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4001862		19770104
APPLICATION INFO.:	US 1975-630990		19751112 (5)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1973-409417, filed on 25 Oct 1973, now abandoned		

	NUMBER	DATE
PRIORITY INFORMATION:	NL 1973-3777	19730319

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Wojciechowicz, Edward J.
LEGAL REPRESENTATIVE:	Trifari, Frank R., Oisher, Jack
NUMBER OF CLAIMS:	16
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	13 Drawing Figure(s); 6 Drawing Page(s)
LINE COUNT:	703

AB Variable capacitance bucket brigade memory in which variable capacitances are used instead of fixed capacitances in order to reduce the Signal-Step-Response-Error.

L4 ANSWER 41 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER:	2002:313309 BIOSIS
DOCUMENT NUMBER:	PREV200200313309
TITLE:	VEGFR-2 (Flk-1) and the adherens junction serve as laminar shear stress co-receptors in vascular endothelial cells.
AUTHOR(S):	Shay-Salit, Ayelet (1); Shushy, Moran (1); Wolfovitz, Efrat (1); Dejana, Elizabetta; Ferruccio, Brava; Resnick, Nitzan
CORPORATE SOURCE:	(1) Faculty of Medicine, Department of Anatomy and Cell biology, Technion Israel Institute of Technology and Rappaport Research Institute., Bat-Galim, Haifa, 31096 Israel
SOURCE:	FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A200. http://www.fasebj.org/. print. Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002 ISSN: 0892-6638.
DOCUMENT TYPE:	Conference
LANGUAGE:	English

AB Blood flow interactions with the vascular endothelium represents a specialized example of mechanical regulation of cell function that has

important physiological and pathophysiological consequences. Yet, the mechanisms of mechanostransduction into these cells are not fully understood. The present study focused on the adherens junction and its role in shear stress sensing. This study shows that although the level of both VE-cadherin and b-catenin does not change in vascular endothelial cells exposed to laminar shear stress, a rapid and transient increase in the VE-cadherin - cytoskeleton-bound fraction occurs, accompanied by a simultaneous increase in the binding of VE-cadherin to b-catenin. Interestingly, in the same time frame a rapid and transient increase occurs in the levels of the cytoskeleton-bound fractions of the VEGFR-2 and in its binding to the adherens complex. Endothelial cells lacking the gene for VE-cadherin failed to transduce shear stress signals such as the phosphorylation of Akt1 or the induced expression of a luciferase gene regulated by an **SSRE** (**Shear Stress Response element**) -hybrid promoter. Thus, these results suggest for the first time that VEGF receptor 2 and the adherens junction molecules VE-cadherin and b-catenin act as shear stress co-receptors and point at their possible role in fluid shear stress mechanotransduction.

L4 ANSWER 42 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:252364 BIOSIS
DOCUMENT NUMBER: PREV200200252364
TITLE: Regulation of nitric oxide synthesis by abnormal extracellular matrix proteins: A possible role for STAT5 as a target for this modulation.
AUTHOR(S): Gonzalez-Santiago, Laura (1); Lopez-Ongil, Susana (1); Martinez Torres, Juan Angel (1); Lucio-Cazana, Javier (1); Rodriguez-Puyol, Manuel (1); Rodriguez-Puyol, Diego
CORPORATE SOURCE: (1) Physiology Dpt., Alcala University, Alcala de Henares, Madrid Spain
SOURCE: Journal of the American Society of Nephrology, (September, 2000) Vol. 11, No. Program and Abstract Issue, pp. 527A-528A. http://www.jasn.org/. print.
Meeting Info.: 33rd Annual Meeting of the American Society of Nephrology and the 2000 Renal Week Toronto, Ontario, Canada October 10-16, 2000
ISSN: 1046-6673.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 43 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:303859 BIOSIS
DOCUMENT NUMBER: PREV200000303859
TITLE: Mapping of a shear stress responsive element (**SSRE**) in the rat angiotensin I converting enzyme gene.
AUTHOR(S): Miyakawa, A. A. (1); Krieger, J. E. (1)
CORPORATE SOURCE: (1) Lab. Gen. Mol. Cardiology, Medicine/LIM13, Heart Institute, Univ Sao Paulo Medl Sch, Sao Paulo, SP Brazil
SOURCE: FASEB Journal, (March 15, 2000) Vol. 14, No. 4, pp. A413. print.
Meeting Info.: Annual Meeting of Professional Research Scientists: Experimental Biology 2000 San Diego, California, USA April 15-18, 2000 Federation of American Societies for Experimental Biology
. ISSN: 0892-6638.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L4 ANSWER 44 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:508377 BIOSIS
DOCUMENT NUMBER: PREV199900508377
TITLE: Requirement of GATA binding proteins for induction of endothelial nitric oxide synthase gene transcription by laminar flow.

AUTHOR(S): La Fata, Vito (1); Laufs, Ulrich (1); Spiecker, Martin (1);
Peng, Ha[redacted]bing (1); Liu, Feng (1); Sessa, lliam C.; Shyy,
John; Liao, James K. (1)
CORPORATE SOURCE: (1) Brigham and Women's Hosp., Boston, MA USA
SOURCE: Circulation, (Oct. 27, 1998) Vol. 98, No. 17 SUPPL., pp. I312.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association
. ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 45 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:511183 BIOSIS
DOCUMENT NUMBER: PREV199799810386
TITLE: Effects of fluid shear stress on atherogenesis and hemostasis.
AUTHOR(S): Ruef, J.; Bode, C.; Runge, M. S. (1)
CORPORATE SOURCE: (1) Div. Cardiology, Univ. Texas Med. Branch, 5.106 John Sealy Hosp., 301 University Blvd., Galveston, TX 77555-0553
USA
SOURCE: Fibrinolysis & Proteolysis, (1997) Vol. 11, No. SUPPL. 2, pp. 159-164.
DOCUMENT TYPE: Journal; Article
LANGUAGE: English

L4 ANSWER 46 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:48807 BIOSIS
DOCUMENT NUMBER: PREV199698620942
TITLE: Endothelial glycoprotein (Gp)Ib-alpha expression is upregulated by arterial shear stress.
AUTHOR(S): Beacham, D. A.; Tran, L.-P.; Ludlow, L. B.; Huang, R.; Konkle, B. A.; Shapiro, S. S.
CORPORATE SOURCE: Cardeza Foundation Hematologic Research, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA USA
SOURCE: Blood, (1995) Vol. 86, No. 10 SUPPL. 1, pp. 281A.
Meeting Info.: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L4 ANSWER 47 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:329706 BIOSIS
DOCUMENT NUMBER: PREV199598344006
TITLE: Endothelial gene regulation by biomechanical forces.
AUTHOR(S): Resnick, Nitzan (1); Bauer, Sumpio E.; Du, Wei; Gimbrone, Michael A., Jr.
CORPORATE SOURCE: (1) Vasc. Res. Div., Dep. Pathol., Brigham and Women's Hosp., 221 Longwood Ave., Boston, MA 02115-5817 USA
SOURCE: Woodford, F. P. [Editor]; Davignon, J. [Editor]; Sniderman,
A. [Editor]. International Congress Series, (1995) No. 1066, pp. 838-843. International Congress Series; Atherosclerosis X.
Publisher: Elsevier Science Publishers B.V. PO Box 211, Sara Burgerhartstraat 25, 1000 AE Amsterdam, Netherlands.
Meeting Info.: 10th International Symposium Montreal, Quebec, Canada October 9-14, 1994
ISSN: 0531-5131. ISBN: 0-444-82007-8.
DOCUMENT TYPE: Book; Conference
LANGUAGE: English

L4 ANSWER 48 OF 48 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:19[illegible]8 BIOSIS
DOCUMENT NUMBER: PREV199598208458
TITLE: Nuclear factor-kappa-B interacts functionally with the **shear-stress-response-element** in the platelet-derived growth factor B-chain promoter.
AUTHOR(S): Khachigian, Levon M. (1); Resnick, Nitzan; Gimbrone., Michael A., Jr.; Collins, Tucker
CORPORATE SOURCE: (1) Vascular Res. Div., Dep. Pathol., Brigham and Women's Hosp., Boston, MA 02115 USA
SOURCE: FASEB Journal, (1995) Vol. 9, No. 3, pp. A412.
Meeting Info.: Experimental Biology 95, Part I Atlanta, Georgia, USA April 9-13, 1995
ISSN: 0892-6638.

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=> e dzau ?/au

E1            2     DZATOR J A/AU
E2            1     DZATSOKHOV S V/AU
E3            0 --> DZAU ?/AU
E4            2     DZAU J/AU
E5            1     DZAU JACQUELINE/AU
E6            2     DZAU R E/AU
E7           51     DZAU V/AU
E8            2     DZAU V I/AU
E9         1180     DZAU V J/AU
E10          11     DZAU V J */AU
E11          18     DZAU VICTOR/AU
E12         560     DZAU VICTOR J/AU

=> s e7-e12

L5         1818 ("DZAU V"/AU OR "DZAU V I"/AU OR "DZAU V J"/AU OR "DZAU V J
                *"/AU OR "DZAU VICTOR"/AU OR "DZAU VICTOR J"/AU)

=> s l5 and decoy

L6           75 L5 AND DECOY

=> dup rem l6

PROCESSING COMPLETED FOR L6
L7            34 DUP REM L6 (41 DUPLICATES REMOVED)

=> d l7 ibib abs tot


L7   ANSWER 1 OF 34      MEDLINE
ACCESSION NUMBER:    2002345956      MEDLINE
DOCUMENT NUMBER:     22083661   PubMed ID: 12089058
TITLE:               Transcription factor decoy.
COMMENT:             Comment on: Circ Res. 2002 Jun 28;90(12):1325-32
AUTHOR:              Dzau Victor J
CONTRACT NUMBER:     HL 35610 (NHLBI)
     HL 54527 (NHLBI)
     HL 59316 (NHLBI)
SOURCE:              CIRCULATION RESEARCH, (2002 Jun 28) 90 (12) 1234-6.
                     Journal code: 0047103. ISSN: 1524-4571.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Commentary
                     Editorial
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200207
ENTRY DATE:          Entered STN: 20020629
                     Last Updated on STN: 20020717
                     Entered Medline: 20020716

L7   ANSWER 2 OF 34  USPATFULL
ACCESSION NUMBER:        2002:99432  USPATFULL
TITLE:                   Therapeutic use of cis-element decoys in vivo
INVENTOR(S):             Dzau, Victor J., Los Altos Hills, CA, UNITED
                         STATES
                         Gibbons, Gary H., Palo Alto, CA, UNITED STATES
                         Morishita, Ryuichi, Palo Alto, CA, UNITED STATES
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	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002052333	A1	20020502
APPLICATION INFO.:	US 2001-839752	A1	20010419 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1995-524206, filed on 8 Sep
1995, PENDING Continuation of Ser. No. US 1993-144717, filed on 29 Oct 1993, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CLARK & ELBING LLP, 176 FEDERAL STREET, BOSTON, MA, 02110-2214
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 689
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides for the use of oligodeoxynucleotide decoys for the prophylactic or therapeutic treatment of diseases associated with the binding of endogenous transcription factors to genes involved in cell growth, differentiation and signalling or to viral genes. By inhibiting endogenous trans-activating factors from binding transcription regulatory regions, the decoys modulate gene expression and thereby regulating pathological processes including inflammation, intimal hyperplasia, angiogenesis, neoplasia, immune responses and viral infection. The decoys are administered in amounts and under conditions whereby binding of the endogenous transcription factor to the endogenous gene is effectively competitively inhibited without significant host toxicity. The subject compositions comprise the **decoy** molecules in a context which provides for pharmacokinetics sufficient for effective therapeutic use.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 3 OF 34 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2002207084 MEDLINE
DOCUMENT NUMBER: 21937877 PubMed ID: 11940548
TITLE: Endothelial healing in vein grafts: proliferative burst unimpaired by genetic therapy of neointimal disease.
AUTHOR: Ehsan Afshin; Mann Michael J; Dell'Acqua Giorgio; Tamura Koichi; Braun-Dullaeus Ruediger; **Dzau Victor J**
CORPORATE SOURCE: Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Mass 02115, USA.
CONTRACT NUMBER: HL-35610 (NHLBI)
HL-58516 (NHLBI)
HL-59316 (NHLBI)
HL-61661 (NHLBI)
SOURCE: CIRCULATION, (2002 Apr 9) 105 (14) 1686-92.
Journal code: 0147763. ISSN: 1524-4539.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020410
Last Updated on STN: 20020413
Entered Medline: 20020412

AB BACKGROUND: Although inhibition of neointimal hyperplasia by cell cycle gene blockade therapy results in improved endothelial cell function in experimental vein grafts, little is known either about endothelial healing immediately after vein grafting or about the effect of this therapy on the

healing process. METHODS AND RESULTS: Scanning electron microscopy demonstrated an immedi[redacted] decrease in vein graft endothe[redacted]al cell density associated with vein g[redacted]t wall stretch, followed by a r[redacted]urn to baseline by postoperative day 3. En face detection of bromodeoxyuridine incorporation confirmed a rapid endothelial proliferation by 48 hours. Despite inhibition of underlying vascular smooth muscle cell proliferation, E2F **decoy** oligonucleotide did not inhibit either endothelial bromodeoxyuridine incorporation or the return to baseline cell density. This differential response to E2F **decoy** was also observed in human umbilical vein endothelial cell culture, which resisted the E2F **decoy** inhibition of cell growth that was observed in human umbilical artery smooth muscle cells, despite evidence for nuclear localized delivery of the oligonucleotide into both cell types. Furthermore, the reduction of E2F binding activity seen in a nuclear gel shift assay of cultured smooth muscle cells was not observed in endothelial cells. CONCLUSIONS: These results suggest a burst of graft endothelial cell proliferation that allows a rapid restoration of cell density in the monolayer. Additionally, there is a selective effect of E2F **decoy** gene therapy on target smooth muscle cells with sparing of this endothelial healing.

L7 ANSWER 4 OF 34 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
ACCESSION NUMBER: 2002:507978 CAPLUS
TITLE: Transcription factor **decoy**
AUTHOR(S): **Dzau, Victor J.**
CORPORATE SOURCE: Department of Medicine, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: Circulation Research (2002), 90(12), 1234-1236
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review on the use of transcription factor **decoy** as a tool to study gene regulation and as exptl. therapy to treat various pathol. conditions. The inhibitory effects of AP-1 **decoy** oligonucleotide on vascular smooth muscle cell proliferation in vitro and neointimal formation in vivo are emphasized.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 34 MEDLINE
ACCESSION NUMBER: 2001275418 MEDLINE
DOCUMENT NUMBER: 21262905 PubMed ID: 11370767
TITLE: Gene therapy for human bypass grafts.
AUTHOR: Mangi A A; **Dzau V J**
SOURCE: ANNALS OF MEDICINE, (2001 Apr) 33 (3) 153-5.
Journal code: 8906388. ISSN: 0785-3890.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Editorial
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20011029
Last Updated on STN: 20011029
Entered Medline: 20011025
AB Autologous saphenous vein is the conduit of choice for the bypass of arterial occlusive disease, be it in the peripheral arterial tree or in the coronary system. This technique is limited by primary graft failure rates approaching 20% in the first year for peripheral arterial disease and 50% at 10 years for coronary artery bypass grafting. The PREVENT trial

describes a novel, safe and effective means of ex vivo transfection of harvested vein grafts with an E2F **decoy** oligonucleotide with 70-74% decreases in the level of proliferating cell nuclear antigen (PCNA) and c-myc mRNA expressed by the smooth muscle cells in the vein. This translated into a statistically significant reduction in primary graft failure when used to bypass peripheral arterial occlusions in a high-risk human patient population.

L7 ANSWER 6 OF 34 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001190262 MEDLINE
DOCUMENT NUMBER: 21176135 PubMed ID: 11279413
TITLE: Long-term stabilization of vein graft wall architecture and prolonged resistance to experimental atherosclerosis after E2F **decoy** oligonucleotide gene therapy.
AUTHOR: Ehsan A; Mann M J; Dell'Acqua G; **Dzau V J**
CORPORATE SOURCE: Division of Cardiovascular Medicine, Brigham and Women's Hospital/Harvard Medical School, 75 Francis Street, Boston, MA 202115, USA.
CONTRACT NUMBER: HL35610 (NHLBI)
HL58516 (NHLBI)
HL59316 (NHLBI)
HL61661 (NHLBI)
SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (2001 Apr) 121 (4) 714-22.
Journal code: 0376343. ISSN: 0022-5223.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

AB OBJECTIVE: We tested the hypothesis that a single intraoperative transfection of rabbit vein grafts with a **decoy** oligonucleotide that blocks cell-cycle gene transactivation by the transcription factor E2F induces long-term stable adaptation that involves medial hypertrophy and a resistance to neointimal hyperplasia and atherosclerosis. METHODS: Jugular vein to carotid artery interposition vein grafts in hypercholesterolemic rabbits were treated, using pressure-mediated delivery, with either E2F **decoy** oligonucleotide, scrambled oligonucleotide, or vehicle alone. E2F **decoy** inhibition of cell-cycle gene expression was determined by measuring proliferating cell nuclear antigen upregulation and bromodeoxyuridine incorporation in vascular smooth muscle cells. Neointimal hyperplasia and atherosclerosis were compared between groups at 6 months after operation. Wall stress was derived from the ratio of luminal radius to wall thickness. Normal rabbits exposed to 6 weeks of diet-induced hypercholesterolemia starting 6 months after operation were analyzed in the same manner. RESULTS: The E2F **decoy** oligonucleotide, but not scrambled oligonucleotide or vehicle alone, inhibited proliferating cell nuclear antigen expression and smooth muscle cell proliferation. Furthermore, this manipulation of cell-cycle gene expression yielded an inhibition of neointimal hyperplasia and atherosclerotic plaque formation throughout the 6 months of cholesterol feeding. In normocholesterolemic rabbits, vehicle-treated and scrambled oligonucleotide-treated vein grafts remain susceptible to diet-induced atherosclerosis as well, whereas resistance to this disease induction remained stable in genetically engineered grafts. CONCLUSION: A single intraoperative pressure-mediated delivery of E2F **decoy** effectively provides vein grafts with long-term resistance to neointimal

hyperplasia and atherosclerosis. These findings suggest that long-term reduction in human vein graft failure rates may be feasible with this ex vivo gene therapy approach.

L7 ANSWER 7 OF 34 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4
ACCESSION NUMBER: 2001169921 EMBASE
TITLE: Gene therapy for human bypass grafts.
AUTHOR: Mangi A.A.; **Dzau V.J.**
CORPORATE SOURCE: Dr. V.J. Dzau, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115-6195, United States. vdzau@parmers.org
SOURCE: Annals of Medicine, (2001) 33/3 (153-155).
Refs: 14
ISSN: 0785-3890 CODEN: ANMDEU
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Autologous saphenous vein is the conduit of choice for the bypass of arterial occlusive disease, be it in the peripheral arterial tree or in the coronary system. This technique is limited by primary graft failure rates approaching 20% in the first year for peripheral arterial disease and 50% at 10 years for coronary artery bypass grafting. The PREVENT trial
describes a novel, safe and effective means of ex vivo transfection of harvested vein grafts with an E2F **decoy** oligonucleotide, with 70-74% decreases in the level of proliferating cell nuclear antigen (PCNA)
and c-myc mRNA expressed by the smooth muscle cells in the vein. This translated into a statistically significant reduction in primary graft failure when used to bypass peripheral arterial occlusions in a high-risk human patient population.

L7 ANSWER 8 OF 34 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2000409975 MEDLINE
DOCUMENT NUMBER: 20379252 PubMed ID: 10918504
TITLE: Transcription factor **decoy** for NFkappaB inhibits TNF-alpha-induced cytokine and adhesion molecule expression
in vivo.
AUTHOR: Tomita N; Morishita R; Tomita S; Gibbons G H; Zhang L; Horiuchi M; Kaneda Y; Higaki J; Ogihara T; **Dzau V J**
CORPORATE SOURCE: Department of Geriatric Medicine, Osaka University Medical School, Japan.
CONTRACT NUMBER: HL 35252 (NHLBI)
HL 35610 (NHLBI)
HL 42663 (NHLBI)
SOURCE: GENE THERAPY, (2000 Aug) 7 (15) 1326-32.
Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907
Last Updated on STN: 20000907
Entered Medline: 20000828
AB The expression of several cytokines and adhesion molecules is regulated by
the transcription factor NFkappaB, which is activated by tumor necrosis factor alpha (TNF-alpha). In this study, we employed a mouse model of nephritis induced by TNF-alpha to examine whether inhibition of NFkappaB activity using transcription factor **decoy** oligonucleotides (ODN) blocks cytokine and adhesion molecule expression and attenuates the renal

inflammatory response. First, we developed a method for delivering FITC-ODN in vivo into mouse kidney glomeruli by employing HVJ-liposome. Then, in order to study the feasibility of **decoy** strategy in vivo, the reporter gene chloramphenicol acetyltransferase (CAT) driven by three tandemly repeated NFkappaB binding sequences was transfected into the kidney. Intrapenetorial injection of TNF-alpha stimulated CAT expression in vivo, and the increase in CAT expression was completely abolished by NFkappaB **decoy** ODN, but not scrambled ODN. Therefore, we examined the effect of NFkappaB **decoy** ODN transfection on TNF-alpha-induced endogenous interleukin (IL)-1alpha, IL-1beta, IL-6, ICAM-1 and VCAM-1 gene expression as assessed by RT-PCR and Northern blotting. Our present data showed that NFkappaB **decoy** , but not scrambled, ODN abolished TNF-alpha induced gene expression in vivo, as well as glomerular inflammation as assessed by CD45 staining. Taken together, our results suggest the potential utility of NFkappaB **decoy** strategy for molecular therapy to glomerular inflammatory diseases.

L7 ANSWER 9 OF 34 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2001046157 MEDLINE
DOCUMENT NUMBER: 20521679 PubMed ID: 11067859
TITLE: Therapeutic applications of transcription factor **decoy** oligonucleotides.
AUTHOR: Mann M J; **Dzau V J**
CORPORATE SOURCE: Department of Surgery, and. Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: HL-35610 (NHLBI)
HL-58516 (NHLBI)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (2000 Nov) 106 (9) 1071-5. Ref: 42
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001206

L7 ANSWER 10 OF 34 USPATFULL
ACCESSION NUMBER: 1999:78692 USPATFULL
TITLE: Intracellular delivery of nucleic acids using pressure
INVENTOR(S): Mann, Michael J., Newton, MA, United States
Diet, Frank P., Koln, Germany, Federal Republic of
Dzau, Victor J., Newton, MA, United States
Gibbons, Gary H., Lexington, MA, United States
Von Der Leyen, Heiko, Sehnde, Germany, Federal Republic of
PATENT ASSIGNEE(S): Board of Trustees of the Leland Stanford Junior University, Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5922687		19990713
APPLICATION INFO.:	US 1996-745023		19961107 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1995-434750, filed on 4 May 1995
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ketter, James

ASSISTANT EXAMINER: Yucel, Irem
LEGAL REPRESENTATIVE: Clark & Elbing LLP
NUMBER OF CLAIMS: 90
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 32 Drawing Figure(s); 15 Drawing Page(s)
LINE COUNT: 1091
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Naked nucleic acids (DNA, RNA, and/or analogs), drugs, and/or other molecules in an extracellular environment enter cells in living intact tissue upon application of pressure to the cells and extracellular environment. Nucleic acids localize to the cell nuclei. Transfection efficiencies greater than 90% are achievable for naked DNA and RNA. A sealed enclosure, defined by an enclosing means and/or tissue, contains the cells and their extracellular environment. The enclosure is pressurized to an incubation pressure on the order of atmospheres. A protective inelastic sheath may be used to prevent distension and trauma in tissue that is part of the enclosure boundary. Suitable enclosures include pressurization chambers and organs such as blood vessels or the heart. Parts of organs, entire organs, and/or entire organisms are pressurized. Suitable target tissue types include blood vessel (in particular vein) tissue, heart, kidney, liver, and bone marrow tissue. Gene therapy applications include ex-vivo treatment of grafts prior to transplantation, and in-vivo treatment of tissue. Useful therapy targets include cell cycle regulatory genes for blocking cell proliferation, and interleukin (IL) and cell adhesion molecule (CAM) genes for reducing immune responses to grafts.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L7 ANSWER 11 OF 34 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999272707 MEDLINE
DOCUMENT NUMBER: 99272707 PubMed ID: 10339601
TITLE: Pressure-mediated oligonucleotide transfection of rat and human cardiovascular tissues.
AUTHOR: Mann M J; Gibbons G H; Hutchinson H; Poston R S; Hoyt E G; Robbins R C; **Dzau V J**
CORPORATE SOURCE: Division of Cardiovascular Medicine, Brigham and Women's Hospital/Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 May 25) 96 (11) 6411-6. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990712
Last Updated on STN: 19990712
Entered Medline: 19990624

AB The application of gene therapy to human disease is currently restricted by the relatively low efficiency and potential hazards of methods of oligonucleotide or gene delivery. Antisense or transcription factor **decoy** oligonucleotides have been shown to be effective at altering gene expression in cell culture expreriments, but their in vivo application is limited by the efficiency of cellular delivery, the intracellular stability of the compounds, and their duration of activity. We report herein the development of a highly efficient method for naked oligodeoxynucleotide (ODN) transfection into cardiovascular tissues by using controlled, nondistending pressure without the use of viral vectors, lipid formulations, or exposure to other adjunctive, potentially hazardous

substances. In this study, we have documented the ability of ex vivo, pressure-mediated transfection to achieve nuclear localization of fluorescent (FITC)-labeled ODN in approximately 90% and [redacted] of cells in intact human saphenous vein and rat myocardium, respectively. We have further documented that pressure-mediated delivery of antisense ODN can functionally inhibit target gene expression in both of these tissues in a sequence-specific manner at the mRNA and protein levels. This oligonucleotide transfection system may represent a safe means of achieving the intraoperative genetic engineering of failure-resistant human bypass grafts and may provide an avenue for the genetic manipultation of cardiac allograft rejection, allograft vasculopathy, or other transplant diseases.

L7 ANSWER 12 OF 34 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2000017656 MEDLINE
DOCUMENT NUMBER: 20017656 PubMed ID: 10551494
TITLE: Ex-vivo gene therapy of human vascular bypass grafts with E2F **decoy**: the PREVENT single-centre, randomised, controlled trial.
AUTHOR: Mann M J; Whittemore A D; Donaldson M C; Belkin M; Conte M S; Polak J F; Orav E J; Ehsan A; Dell'Acqua G; **Dzau V J**
CORPORATE SOURCE: Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA.
SOURCE: LANCET, (1999 Oct 30) 354 (9189) 1493-8.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991118

AB BACKGROUND: Cell-cycle blockade by ex-vivo gene therapy of experimental vein grafts inhibits the neointimal hyperplasia and subsequent accelerated atherosclerosis that lead to human bypass-graft failure. In a prospective, randomised, controlled trial, we investigated the safety and biological efficacy of intraoperative gene therapy in patients receiving bypass vein grafts. METHODS: We studied gene therapy that uses **decoy** oligodeoxynucleotide, which binds and inactivates the pivotal cell-cycle transcription factor E2F. 41 patients were randomly assigned untreated (16), E2F-**decoy**-treated (17), or scrambled-oligodeoxynucleotide-treated (eight) human infrainguinal vein grafts. Oligonucleotide was delivered to grafts intraoperatively by ex-vivo pressure-mediated transfection. The primary endpoints were safety and inhibition of target cell-cycle regulatory genes and of DNA synthesis in the grafts. Analysis was by intention to treat. FINDINGS: Mean transfection efficiency was 89.0% (SD 1.9). Proliferating-cell nuclear antigen and c-myc mRNA concentrations and bromodeoxyuridine incorporation were decreased in the EF2-**decoy** group by medians of 73% [IQR 53-84], 70% [50-79], and 74% [56-83], respectively) but not in the scrambled-oligodeoxynucleotide group ($p<0.0001$). Groups did not differ for postoperative complication rates. At 12 months, fewer graft occlusions, revisions, or critical stenoses were seen in the E2F-**decoy** group than in the untreated group (hazard ratio 0.34 [95% CI 0.12-0.99]). INTERPRETATION: Intraoperative transfection of human bypass vein grafts with E2F-**decoy** oligodeoxynucleotide is safe, feasible, and can achieve sequence-specific inhibition of cell-cycle gene expression and DNA replication. Application of this genetic-engineering strategy may lower failure rates of human primary bypass vein grafting.

L7 ANSWER 13 OF 34 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 19992634[redacted] MEDLINE
DOCUMENT NUMBER: 99263422[redacted] PubMed ID: 10325243
TITLE: Transcription factor **decoy** to study the molecular mechanism of negative regulation of renin gene expression in the liver in vivo.
AUTHOR: Tomita S; Tomita N; Yamada T; Zhang L; Kaneda Y; Morishita R; Ogihara T; **Dzau V J**; Horiuchi M
CORPORATE SOURCE: Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard University Medical School, Boston, MA, USA.. tomita@geriat.med.osaka-u.ac.jp
CONTRACT NUMBER: HL07708 (NHLBI)
HL35252 (NHLBI)
HL35610 (NHLBI)
+
SOURCE: CIRCULATION RESEARCH, (1999 May 14) 84 (9) 1059-66.
Journal code: 0047103. ISSN: 0009-7330.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990603

AB Renin is synthesized in high quantities in the juxtaglomerular cells of the kidney, but little or none is synthesized in the liver. Our previous in vitro and biochemical studies have demonstrated that tissue-specific expression of the mouse renin gene is regulated by the specific interaction between negative regulatory element (NRE) in the 5'-flanking region of the renin gene and NRE binding protein (NREB). In this study, we examined the hypothesis that this interaction between the NRE in the promoter region of the rat renin gene and the NREB in the liver contributes to the suppressed renin gene expression in this tissue in vivo. We used in vivo transfection of NRE transcription factor **decoy** (TFD) double-stranded oligonucleotide into the rat liver via portal vein infusion. A gel mobility shift assay showed that transfected NRE TFD blocked endogenous NREB binding with the rat renin gene. This resulted in enhanced hepatic renin mRNA expression, immunohistochemical detection of renin in the liver, and consequently, increased plasma renin concentration. Taken together, these results document the importance of NREB in the inhibition of renin gene expression in rat liver in vivo and suggest the possibility of in vivo renin gene modulation by the TFD approach.

L7 ANSWER 14 OF 34 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:15350 CAPLUS
DOCUMENT NUMBER: 132:206345
TITLE: Possible E2F-independent cell cycle progression in the endothelium of genetically engineered grafts
AUTHOR(S): Ehsan, Afshin; Mann, Michael J.; Dell'Acqua, Giorgio; Braun-Dullaeus, Ruediger; **Dzau, Victor J.**
CORPORATE SOURCE: Research Institute and Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA
SOURCE: Surgical Forum (1999), 50, 421-423
CODEN: SUFOAX; ISSN: 0071-8041
PUBLISHER: American College of Surgeons
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, the authors investigated the proliferative response of the endothelial monolayer and sought to det. whether this endothelial healing

was adversely affected by treatment with **decoy** oligodeoxynucleotides (ODN) targeting the transcription factor E2F, which is known to arrest cell cycle progression in vascular smooth muscle cells (SMC). An interposition graft of the right jugular vein to the carotid artery led to an acute dilation of the conduit and a subsequent significant increase in surface area. Rapid healing was further demonstrated. E2F **decoy** ODN treatment arrested the growth of quiescent cultured human SMC but not that of human endothelial cells upon restimulation with serum. Despite sequence-specific inhibition of SMC proliferation in vitro and in vivo, E2F **decoy** ODN does not inhibit cell cycle entry and progression of endothelial cells, thus suggesting an E2F-independent pathway for the completion of the cell cycle.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L7 ANSWER 15 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:24884 BIOSIS
DOCUMENT NUMBER: PREV200000024884
TITLE: Ex vivo gene therapy with p53 transcription factor **decoy** attenuates apoptosis and myocardial damage in a rat model of ischemia/reperfusion.
AUTHOR(S): Dell'Acqua, Giorgia (1); Mann, Michael J. (1); Zhang, Lu-Nan (1); Ehsan, Afshin (1); **Dzau, Victor J. (1)**
CORPORATE SOURCE: (1) Brigham and Women's Hosp, Boston, MA USA
SOURCE: Circulation, (Nov. 2, 1999) Vol. 110, No. 18 SUPPL., pp. I.481.
Meeting Info.: 72nd Scientific Sessions of the American Heart Association Atlanta, Georgia, USA November 7-10, 1999
ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 16 OF 34 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998153770 MEDLINE
DOCUMENT NUMBER: 98153770 PubMed ID: 9480814
TITLE: Role of AP-1 complex in angiotensin II-mediated transforming growth factor-beta expression and growth of smooth muscle cells: using **decoy** approach against AP-1 binding site.
AUTHOR: Morishita R; Gibbons G H; Horiuchi M; Kaneda Y; Ogihara T; **Dzau V J**
CORPORATE SOURCE: Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
CONTRACT NUMBER: HL 35252 (NHLBI)
HL 35610 (NHLBI)
HL35610 (NHLBI)
+
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Feb 13) 243 (2) 361-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980410
Last Updated on STN: 20020212
Entered Medline: 19980327

AB The cis element double-stranded oligodeoxynucleotides (ODN) ("**decoy**") approach has enabled us to clarify the responsible elements. Using this approach, we transfected AP-1 **decoy** ODN into VSMC cultured from WKY rats (WKY Adu) which produce latent TGF-beta,

but not active TGF-beta, and Sprague-Dawley rats (CNC) which produce active and latent TGF-b[redacted]a under Ang II-stimulation. AP-[redacted] but not mismatched, **decoy** ODN a[redacted]lished Ang II-stimulated TGF-be[redacted] gene expression and production in both Adu and CNC. However, AP-1 **decoy** did not alter DNA, RNA, and protein synthesis in Adu. In contrast, cell number was increased under Ang II stimulation by AP-1 **decoy** ODN in CNC without significant change in RNA and protein synthesis. These results showed that Ang II stimulated TGF-beta production through the AP-1
complex. In VSMC that produce active TGF-beta (CNC), the AP-1 complex stimulated by Ang II may inhibit cell growth through active TGF-beta production. Overall, this study demonstrates the utility of the **decoy** approach to study the specific function of cis elements in endogenous gene regulation such as Ang II-induced TGF-beta expression.

L7 ANSWER 17 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:514589 BIOSIS
DOCUMENT NUMBER: PREV199900514589
TITLE: The PREVENT Trial of vein graft genetic engineering: Preliminary molecular and clinical findings.
AUTHOR(S): Mann, Michael J.; Whittemore, Anthony D.; Donaldson, Magruder C.; Belkin, Michael A.; Conte, Michael S.; Orav, John; Polak, Joseph F.; **Dzau, Victor J.**
CORPORATE SOURCE: Brigham and Women's Hosp., Boston, MA USA
SOURCE: Circulation, (Oct. 27, 1998) Vol. 98, No. 17 SUPPL., pp. I321.
Meeting Info.: 71st Scientific Sessions of the American Heart Association Dallas, Texas, USA November 8-11, 1998 The American Heart Association
. ISSN: 0009-7322.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 18 OF 34 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1998355909 MEDLINE
DOCUMENT NUMBER: 98355909 PubMed ID: 9691019
TITLE: An oligonucleotide **decoy** for transcription factor E2F inhibits mesangial cell proliferation in vitro.
AUTHOR: Tomita N; Horiuchi M; Tomita S; Gibbons G H; Kim J Y; Baran
D; **Dzau V J**
CORPORATE SOURCE: Department of Medicine, Harvard Medical School, Brigham and
Women's Hospital, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: HL-35252 (NHLBI)
HL-35610 (NHLBI)
HL-46631 (NHLBI)
+
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1998 Aug) 275 (2 Pt 2) F278-84.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980916
AB The transcription factor E2F controls expression of several genes involved
in cell proliferation including c-myc, c-myb, proliferating cell nuclear antigen (PCNA), and cdk2 kinase. Having established that both PCNA and cdk2 kinase are induced in rat mesangial cells (MC) by serum stimulation, we attempted to inhibit MC proliferation in vitro by transfecting these cells with cationic liposomes containing a synthetic double-stranded

oligodeoxynucleotide (ODN) with high affinity for E2F. Using a gel mobility shift assay, we detected increased specific binding of E2F in MC following serum stimulation. This binding was completely inhibited by preincubation of MC nuclear extracts with the double-stranded ODN with high affinity for E2F but not by preincubation with a missense ODN containing two point mutations. MC were also transfected with a luciferase reporter gene construct containing three E2F binding sites. Luciferase activity was enhanced by serum stimulation of MC, and this effect was specifically abolished by cotransfection of MC with E2F **decoy** ODN. Furthermore, RT-PCR analysis revealed that serum-induced upregulation of PCNA and cdk2 kinase gene expression was inhibited by E2F **decoy** ODN transfection but not by transfection of missense ODN. These changes in gene expression were paralleled by a reduction in PCNA and cdk2 kinase protein expression in E2F **decoy** ODN transfected cells. MC number increased following serum stimulation. This effect was blunted by transfection with E2F **decoy** ODN but not by transfection of missense ODN. These data suggest that the transcription factor E2F plays a crucial role in the regulation of MC proliferation and that this factor can be successfully targeted to inhibit MC cell cycle progression.

L7 ANSWER 19 OF 34 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:430251 CAPLUS
DOCUMENT NUMBER: 131:223547
TITLE: Molecular mechanism of tissue-specific renin gene expression
AUTHOR(S): Horiuchi, Masatsugu; Chen, Yuqing E.; **Dzau, Victor J.**
CORPORATE SOURCE: Cardiovascular Research, Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, 02115, USA
SOURCE: Wenner-Gren International Series (1998), 74(Renin-Angiotensin), 13-23
CODEN: WGISEA; ISSN: 1356-0409
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 31 refs. The authors discussed in vitro studies of tissue-specific renin gene expression; in vivo identification of an NRE in the mouse renin gene using direct gene transfer; in vivo silencing effect of the Ren1 NRE in mouse submandibular gland and kidney; use of an in vivo transcriptional factor **decoy** approach to examine tissue-specific renin gene expression in the mouse; in vivo cis and trans interactions of the renin promoter with double-stranded phosphorothioate Ren1 NRE oligonucleotides; consensus silencing effect of related NRE sequences; neg. regulation of renin gene expression in the liver in vivo; specific nuclear protein binding to the rat renin NRE in liver; change in the binding of NREB to NRE after **decoy** transfection; expression of renin mRNA in rat liver; changes in hepatic and plasma renin concns.; NRE in the human renin gene; and cloning of NREB.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 20 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:241759 BIOSIS
DOCUMENT NUMBER: PREV199799540962
TITLE: Intra-operative transfection with E2F **decoy** oligonucleotide yields long term resistance to vein graft atherosclerosis.

AUTHOR(S): Mann, M. J.; Kernoff, R.; **Dzau, V. J.**
CORPORATE SOURCE: Dep. Me[redacted] Brigham and Women's Hosp./Har[redacted]rd Med. Sch., Boston, [redacted]A USA
SOURCE: Journal of Investigative Medicine, (1997) Vol. 45, No. 3, pp. 288A.
Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Medical Research: Biomedicine '97 Medical Research from Bench to Bedside Washington, D.C., USA April 25-27, 1997
ISSN: 1081-5589.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L7 ANSWER 21 OF 34 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 12
ACCESSION NUMBER: 1997:710250 CAPLUS
DOCUMENT NUMBER: 127:355171
TITLE: Vein graft gene therapy using E2F **decoy** oligonucleotides: target gene inhibition in human veins and long-term resistance to atherosclerosis in rabbits
AUTHOR(S): Mann, Michael J.; **Dzau, Victor J.**
CORPORATE SOURCE: Division of Cardiovascular Medicine, Harvard Medical School/Brigham and Women's Hospital, Boston, MA, USA
SOURCE: Surgical Forum (1997), 48, 242-244
CODEN: SUFOAX; ISSN: 0071-8041
PUBLISHER: American College of Surgeons
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Vein graft failures are assocd. with the development of graft neointimal hyperplasia and accelerated atherosclerosis. We have demonstrated that a genetic engineering strategy that blocks cell cycle regulatory gene upregulation using antisense oligonucleotides in rabbits prevents this neointimal hyperplasia and that these modified grafts adapt to the hemodynamic stress of the arterial environment instead via medial hypertrophy. Furthermore, this genetic intervention preserves vein graft endothelial function and yields grafts resistant to diet-induced atherosclerosis. Arrest of vascular smooth muscle cell proliferation requires the simultaneous blockade of at least two cell-cycle regulatory genes; we therefore studied inhibition of the transcription factor E2F, the activation of which is responsible for the upregulated expression of numerous genes required for cell cycle progression, using ex vivo transfection of human vein segments with an E2F **decoy** oligodeoxynucleotide. Because vein graft disease develops over months to years, we further tested the hypothesis that neointimal hyperplasia generates a long-term susceptibility to accelerated vein graft atherosclerosis and that intraoperative, genetic inhibition of vascular smooth muscle cell cell cycle progression can yield a stable shift in graft-adaptive biol. such that a long-term resistance to this disease process is achieved.

L7 ANSWER 22 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:10972 BIOSIS
DOCUMENT NUMBER: PREV199799310175
TITLE: Transcription factor **decoy** for NF-kappa-B inhibits TNF-alpha induced expressions of cytokine and adhesion molecule in mesangial cells.
AUTHOR(S): Tomita, N. (1); Morishita, R.; Gibbons, G. H.; Tomita, S.; Kaneda, Y.; Ogihara, T.; **Dzau, V. J.**
CORPORATE SOURCE: (1) Stanford Univ. Stanford, CA USA
SOURCE: Journal of the American Society of Nephrology, (1996) Vol. 7, No. 9, pp. 1723.
Meeting Info.: 29th Annual Meeting of the American Society of Nephrology New Orleans, Louisiana, USA November 3-6, 1996
ISSN: 1046-6673.

DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L7 ANSWER 23 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:10913 BIOSIS
DOCUMENT NUMBER: PREV199799310116
TITLE: Potential gene therapy for glomerulonephritis: Transfection of NF-kappa-B **decoy** inhibited TNF-alpha induced cytokines and adhesion molecules expression in vivo.
AUTHOR(S): Morishita, R.; Tomita, N.; Gibbons, G. H.; Tomita, S.; Zhang, L.; Kaneda, Y.; Ogihara, T.; **Dzau, V. J.**
CORPORATE SOURCE: Stanford Univ., Stanford, CA USA
SOURCE: Journal of the American Society of Nephrology, (1996) Vol. 7, No. 9, pp. 1711.
Meeting Info.: 29th Annual Meeting of the American Society of Nephrology New Orleans, Louisiana, USA November 3-6, 1996
ISSN: 1046-6673.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L7 ANSWER 24 OF 34 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97110450 MEDLINE
DOCUMENT NUMBER: 97110450 PubMed ID: 8952611
TITLE: In vivo gene transfer and gene modulation in hypertension research.
AUTHOR: **Dzau V J**; Horiuchi M
CORPORATE SOURCE: Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass 02115, USA.
CONTRACT NUMBER: HL-35252 (NHLBI)
HL-35610 (NHLBI)
HL-46631 (NHLBI)
+
SOURCE: HYPERTENSION, (1996 Dec) 28 (6) 1132-7. Ref: 44
Journal code: 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970107

AB Transgenic technologies and homologous recombination approaches have been useful for studying the roles of specific genes in systemic hypertension. Recently, we and others have introduced the use of in vivo gene transfer to study the effects of local gene overexpression or inactivation in hypertension. Using in vivo gene transfer for the blood vessel, we have documented the direct hypertrophic action of local angiotensin and the growth-inhibitory effect of nitric oxide. In vivo gene transfer is also an effective method for discovering the unknown functions of a newly cloned gene. Using this approach, we identified the in vivo growth-inhibitory action of the angiotensin II type 2 receptor. In addition, we have developed a novel strategy using transcriptional factor "**decoy**" oligonucleotides to regulate the interaction of cis- and trans-acting factors involved in the modulation of gene expression in vivo. Thus, the **decoy** approach can "switch" on or off specific genes in selective tissues in vivo, thereby influencing local gene expression and tissue function. For example, using **decoy** oligonucleotides, we have "turned on" renin gene expression in the rat liver, in which it is usually not expressed, resulting in increased hepatic and plasma renin levels.

Thus, in vivo gene transfer technology provides us with a new tool for in vivo characterization of genes involved in hypertension that has potential application in human therapy.

L7 ANSWER 25 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:305832 BIOSIS
DOCUMENT NUMBER: PREV199699028188
TITLE: Potential gene therapy using E2F **decoy** approach with HVJ-liposome method to glomerulonephritis in rats.
AUTHOR(S): Tomita, N. (1); Gibbons, G. H. (1); Kim, J. (1); Tomita, S. (1); Zhang, L. (1); Kaneda, Y.; Baran, D.; **Dzau, V. J. (1)**
CORPORATE SOURCE: (1) Stanford Univ., Stanford, CA USA
SOURCE: Journal of Investigative Medicine, (1996) Vol. 44, No. 3, pp. 319A.
Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Clinical Research: Biomedicine '96, Medical Research from Bench to Bedside Washington, D.C., USA May 3-6, 1996
ISSN: 1081-5589.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 26 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:305615 BIOSIS
DOCUMENT NUMBER: PREV199699027971
TITLE: Potential gene therapy for glomerulonephritis: Transfection of NF-kappa-B **decoy** inhibited TNF-alpha induced cytokine and adhesion molecules expression in vivo.
AUTHOR(S): Tomita, N. (1); Morishita, R. (1); Gibbons, G. H. (1); Tomita, S. (1); Horiuchi, M. (1); Zhang, L. (1); Kaneda, Y.; Ogihara, T.; **Dzau, V. J. (1)**
CORPORATE SOURCE: (1) Stanford Univ., Stanford, CA USA
SOURCE: Journal of Investigative Medicine, (1996) Vol. 44, No. 3, pp. 281A.
Meeting Info.: Annual Meeting of the Association of American Physicians, the American Society for Clinical Investigation, and the American Federation for Clinical Research: Biomedicine '96, Medical Research from Bench to Bedside Washington, D.C., USA May 3-6, 1996
ISSN: 1081-5589.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 27 OF 34 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:753502 CAPLUS
DOCUMENT NUMBER: 123:208768
TITLE: In vivo therapeutic use of oligonucleotide cis-element decoys for transcription factor binding
INVENTOR(S): **Dzau, Victor J.**; Gibbons, Gary H.; Morishita, Ryuichi
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9511687 A1 19950504 WO 1994-US12339 19941028
W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, , NL, PT, SE
EP 732929 A1 19960925 EP 1995-900450 19941028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
US 2002052333 A1 20020502 US 2001-839752 20010419
PRIORITY APPLN. INFO.: US 1993-144717 A 19931029
WO 1994-US12339 W 19941028
US 1995-524206 A1 19950908

AB Oligodeoxynucleotide decoys are provided for prophylactic or therapeutic treatment of diseases assocd. with the binding of endogenous transcription factors to genes involved in cell growth, differentiation, and signaling, or to viral genes. By inhibiting endogenous trans-activating factors from binding transcription regulatory regions, the decoys modulate gene expression and thereby regulate pathol. processes including inflammation, intimal hyperplasia, angiogenesis, neoplasia, immune responses, and viral infection. The decoys are administered in amts. and under conditions whereby binding of the endogenous transcription factor to the endogenous gene is effectively competitively inhibited without significant host toxicity. The subject compns. comprise the **decoy** mols. in a context which provides for pharmacokinetics sufficient for effective therapeutic use. Thus, a 14-bp double-stranded DNA oligonucleotide (5'-CTAGATTTCCCGCG-3'/3'-TAAAGGGCGCCTAG-5') was transfected into vascular smooth muscle cells and shown to effectively abolish the binding of the E2F transcription factor to a specific binding site in serum-stimulated cells. Induction of c-myc, cdc2, and PCNA mRNA expression in response to serum stimulation was markedly inhibited by transfection of the E2F **decoy**, whereas there was no effect on .beta.-actin mRNA expression. Phosphatidylserine/phosphatidylcholine/cholesterol liposomes contg. inactivated hemagglutinating virus of Japan (Z strain) were used to encapsulate the dsDNA decoys, resulting in a more rapid cellular uptake and nuclear concn., and a 100-fold higher transfection efficiency than lipofection or passive uptake methods. Neg. response element (NRE):NRE-binding protein interaction responsible for silencing of renin Ren1 gene expression was also affected by dsDNA decoys in cell line (SCA-9) derived from a submandibular gland tumor.

L7 ANSWER 28 OF 34 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 95320174 MEDLINE
DOCUMENT NUMBER: 95320174 PubMed ID: 7597041
TITLE: A gene therapy strategy using a transcription factor **decoy** of the E2F binding site inhibits smooth muscle proliferation in vivo.
AUTHOR: Morishita R; Gibbons G H; Horiuchi M; Ellison K E; Nakama M; Zhang L; Kaneda Y; Ogihara T; **Dzau V J**
CORPORATE SOURCE: Division of Cardiovascular Medicine, Falk Cardiovascular Research Center, Stanford University School of Medicine, CA 94305-5246, USA.
CONTRACT NUMBER: HL35252 (NHLBI)
HL35610 (NHLBI)
HL46631 (NHLBI)
+
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Jun 20) 92 (13) 5855-9. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950817

Last Updated on STN: 19950817
Entered Medline: 19950803

AB The application of DNA technology to regulate the trans ption of disease-related genes in vivo has important therapeutic potentials. The transcription factor E2F plays a pivotal role in the coordinated transactivation of cell cycle-regulatory genes such as c-myc, cdc2, and the gene encoding proliferating-cell nuclear antigen (PCNA) that are involved in lesion formation after vascular injury. We hypothesized that double-stranded DNA with high affinity for E2F may be introduced in vivo as a **decoy** to bind E2F and block the activation of genes mediating cell cycle progression and intimal hyperplasia after vascular injury. Gel mobility-shift assays showed complete competition for E2F binding protein by the E2F **decoy**. Transfection with E2F **decoy** inhibited expression of c-myc, cdc2, and the PCNA gene as well as vascular smooth muscle cell proliferation both in vitro and in the in vivo model of rat carotid injury. Furthermore, 2 weeks after in vivo transfection, neointimal formation was significantly prevented by the E2F **decoy**, and this inhibition continued up to 8 weeks after a single transfection in a dose-dependent manner. Transfer of an E2F **decoy** can therefore modulate gene expression and inhibit smooth muscle proliferation and vascular lesion formation in vivo.

L7 ANSWER 29 OF 34 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 95386676 MEDLINE
DOCUMENT NUMBER: 95386676 PubMed ID: 7657796
TITLE: In vivo identification of a negative regulatory element in the mouse renin gene using direct gene transfer.
AUTHOR: Yamada T; Horiuchi M; Morishita R; Zhang L; Pratt R E; **Dzau V J**
CORPORATE SOURCE: Falk Cardiovascular Research Center, Stanford University School of Medicine, California 94305-5246, USA.
CONTRACT NUMBER: HL-35252 (NHLBI)
HL-35610 (NHLBI)
HL-46631 (NHLBI)
+
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1995 Sep) 96 (3) 1230-7.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951013
Last Updated on STN: 19980206
Entered Medline: 19951004

AB DBA/2J mouse contains two renin gene loci (Ren1d and Ren2d). Ren2d but not Ren1d is expressed in submandibular gland (SMG) while both are expressed in the kidney. Based on vitro studies, we have postulated that a negative regulatory element (NRE) in the renin gene promoter is involved in its tissue-specific expression. In this study, we examined the molecular mechanism at the in vivo level using direct gene transfer. Fragments of the Ren1d or Ren2d promoter were fused to a chloramphenicol acetyltransferase (CAT) gene expression vector. These constructs complexed in fusogenic liposomes were injected directly into the mouse SMG or intraarterially into the mouse kidney via the renal artery. The vector containing the CAT exhibited readily detectable in vivo expressions in both SMG and kidney. In the SMG, Ren1d fragment containing the NRE abolished CAT expression while deletion of the NRE restored CAT expression. The homologous fragment from the Ren2d promoter did not inhibit CAT expression while deletion of the 150-bp insertion resulted in the inhibition. Cotransfection of Ren1d construct with Ren1d-NRE oligonucleotides as transcriptional factor **decoy** restored CAT

expression. Contrary to the SMG, transfection with Ren1d fragment-CAT construct or Ren2d fragment-CAT construct into the kidney resulted in similar levels of CAT expression. Interestingly, human c-myc NRE oligonucleotides which share homology with Ren1d-NRE competed effectively with these oligonucleotides for the regulation of Ren1d gene expression in vivo. This NRE sequence is also homologous to silencer elements found in multiple mammalian genes, suggesting the presence of a family of NRE/NRE binding proteins regulating expression of diverse genes.

L7 ANSWER 30 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:6615 BIOSIS
DOCUMENT NUMBER: PREV199698578750
TITLE: In vivo gene therapy of anti-Thy 1 nephritis using E2F **decoy** oligonucleotide.
AUTHOR(S): Tomita, N. (1); Kim, J.; Gibbons, G. H.; Baran, D.; Ogborn, M.; Stahl, R. A. K.; Tomita, S.; Zhang, L.; Kaneda, Y.; **Dzau, V. J.**
CORPORATE SOURCE: (1) Stanford Univ., Stanford, CA USA
SOURCE: Journal of the American Society of Nephrology, (1995) Vol. 6, No. 3, pp. 887.
Meeting Info.: Annual Meeting of the American Society of Nephrology San Diego, California, USA November 5-8, 1995
ISSN: 1046-6673.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 31 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1996:6177 BIOSIS
DOCUMENT NUMBER: PREV199698578312
TITLE: Oligonucleotide **decoy** for transcriptional factor E2F inhibits rat mesangial cell proliferation in vitro.
AUTHOR(S): Tomita, N. (1); Kim, J.; Gibbons, G. H.; Baran, D.; Tomita, S.; **Dzau, V. J.**
CORPORATE SOURCE: (1) Stanford Univ., Stanford, CA USA
SOURCE: Journal of the American Society of Nephrology, (1995) Vol. 6, No. 3, pp. 778.
Meeting Info.: Annual Meeting of the American Society of Nephrology San Diego, California, USA November 5-8, 1995
ISSN: 1046-6673.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 32 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:519946 BIOSIS
DOCUMENT NUMBER: PREV199598534246
TITLE: In vivo elucidation of negative regulation of tissue specific renin gene expression by transcriptional factor **decoy** approach.
AUTHOR(S): Tomita, Sawako (1); Tomita, Naruya (1); Yamada, Takehiko (1); Zhang, Lunan (1); Ogihara, Toshio; Kaneda, Yasufumi; Horiuchi, Masatsugu (1); **Dzau, Victor J. (1)**
CORPORATE SOURCE: (1) Stanford Univ., Stanford, CA USA
SOURCE: Hypertension (Dallas), (1995) Vol. 26, No. 3, pp. 555.
Meeting Info.: 49th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research New Orleans, Louisiana, USA September 19-22, 1995
ISSN: 0194-911X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L7 ANSWER 33 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:287637 BIOSIS
DOCUMENT NUMBER: PREV199598301937

TITLE: Elucidation of mechanism of tissue specific renin gene expression in vivo using transcriptional factor **decoy** approach.

AUTHOR(S): Tomita, S. (1); Tomita, N.; Yamada, T.; Zhang, L.; Ogihara, T.; Kaneda, Y.; Horiuchi, M.; **Dzau, V. J.**

CORPORATE SOURCE: (1) Falk Cardiovasc. Res. Cent., Stanford Univ., Stanford, CA USA

SOURCE: Journal of Investigative Medicine, (1995) Vol. 43, No. SUPPL. 2, pp. 240A.
Meeting Info.: Clinical Research Meeting San Diego, California, USA May 5-8, 1995

DOCUMENT TYPE: Conference

LANGUAGE: English

L7 ANSWER 34 OF 34 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1995:7879 BIOSIS

DOCUMENT NUMBER: PREV199598022179

TITLE: A novel molecular strategy using cis element "**Decoy** " of E2F binding site inhibits smooth muscle proliferation in vivo.

AUTHOR(S): Morishita, Ryuichi (1); Gibbons, Gary H. (1); Horiuchi, Masatsugu (1); Ellison, Kristin E. (1); Nakajima, Masatoshi (1); Tomita, Naruya (1); Zhang, Lunan (1); Kaneda, Yasufumi; Ogihara, Toshio; **Dzau, Victor J. (1)**

CORPORATE SOURCE: (1) Falk Cardiovascular Res. Cent., Stanford Univ., Stanford, CA USA

SOURCE: Circulation, (1994) Vol. 90, No. 4 PART 2, pp. I191.
Meeting Info.: 67th Scientific Sessions of the American Heart Association Dallas, Texas, USA November 14-17, 1994
ISSN: 0009-7322.

DOCUMENT TYPE: Conference

LANGUAGE: English